Symposium on Endocrinology of Neoplastic Diseases

Vol. 16 JULY, 1944 No. 1

SURGERY

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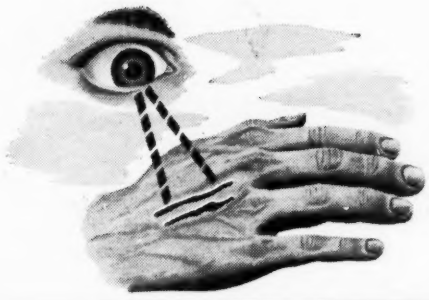

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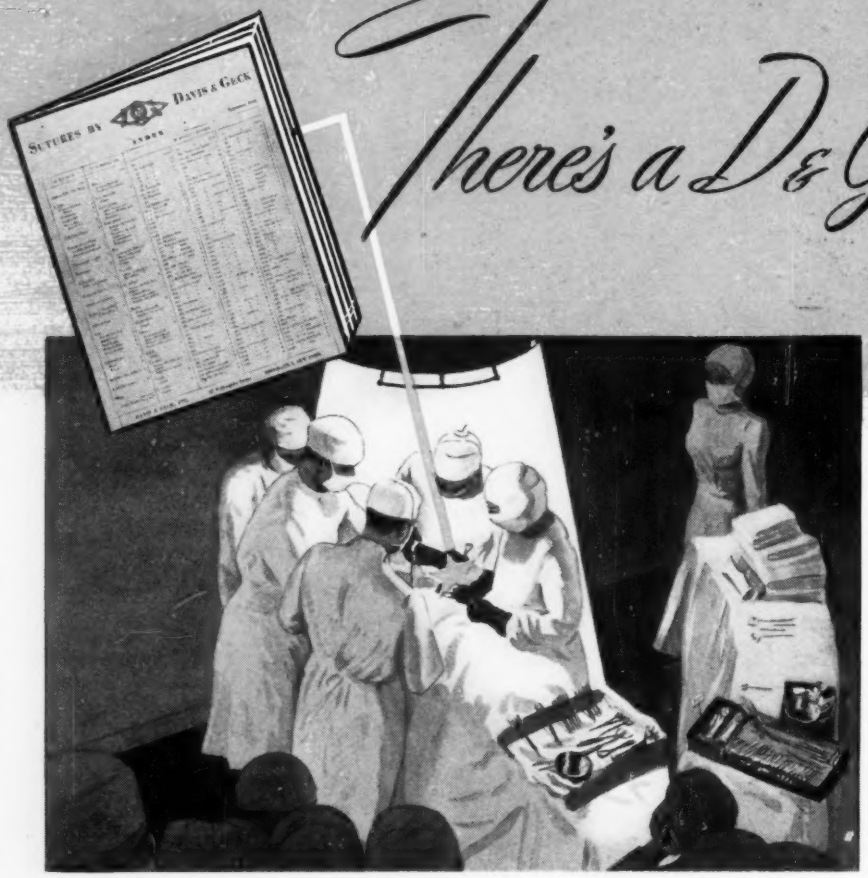

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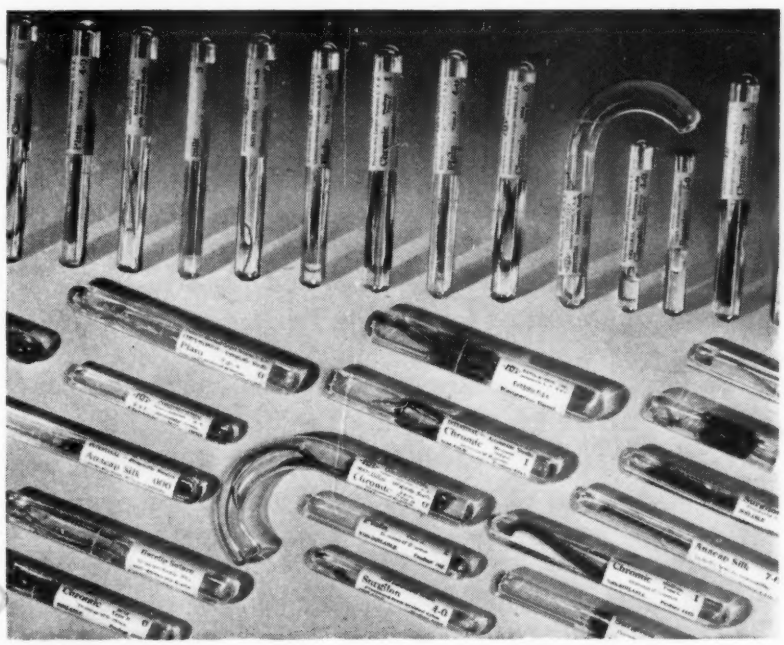

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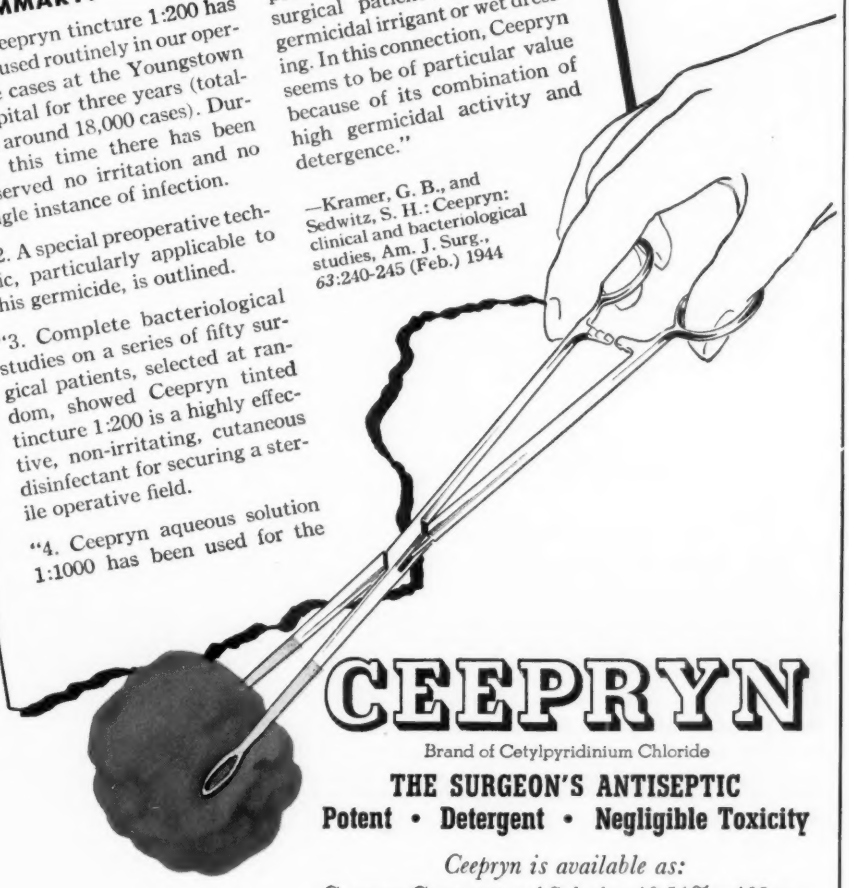

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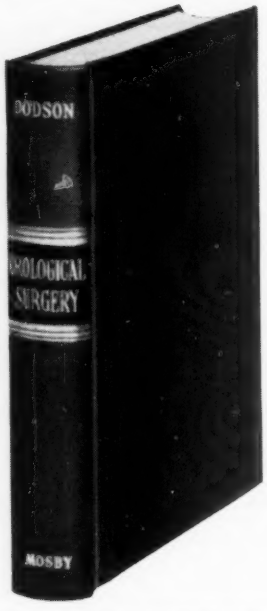

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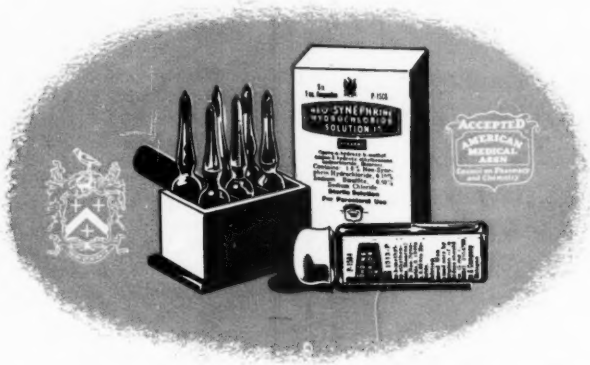

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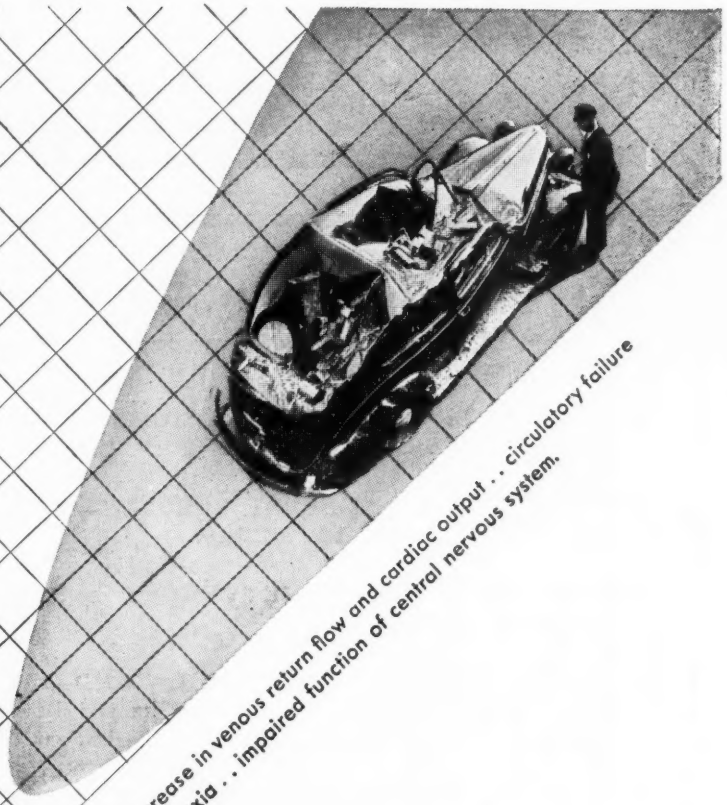

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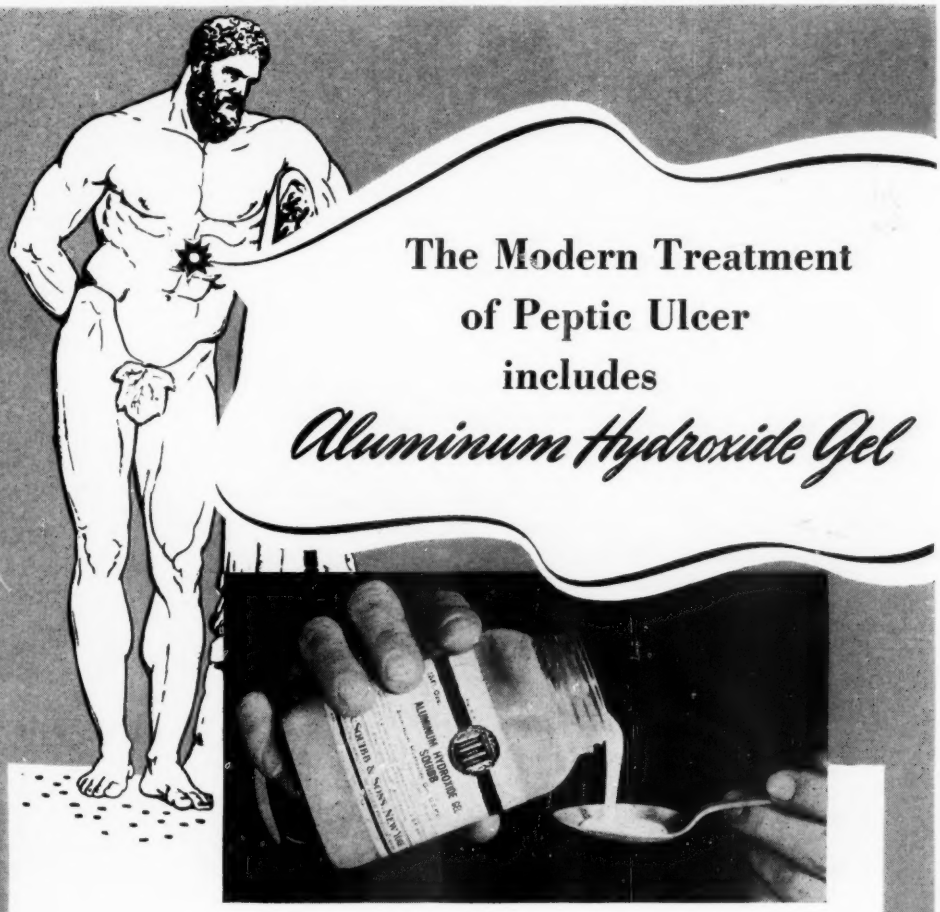

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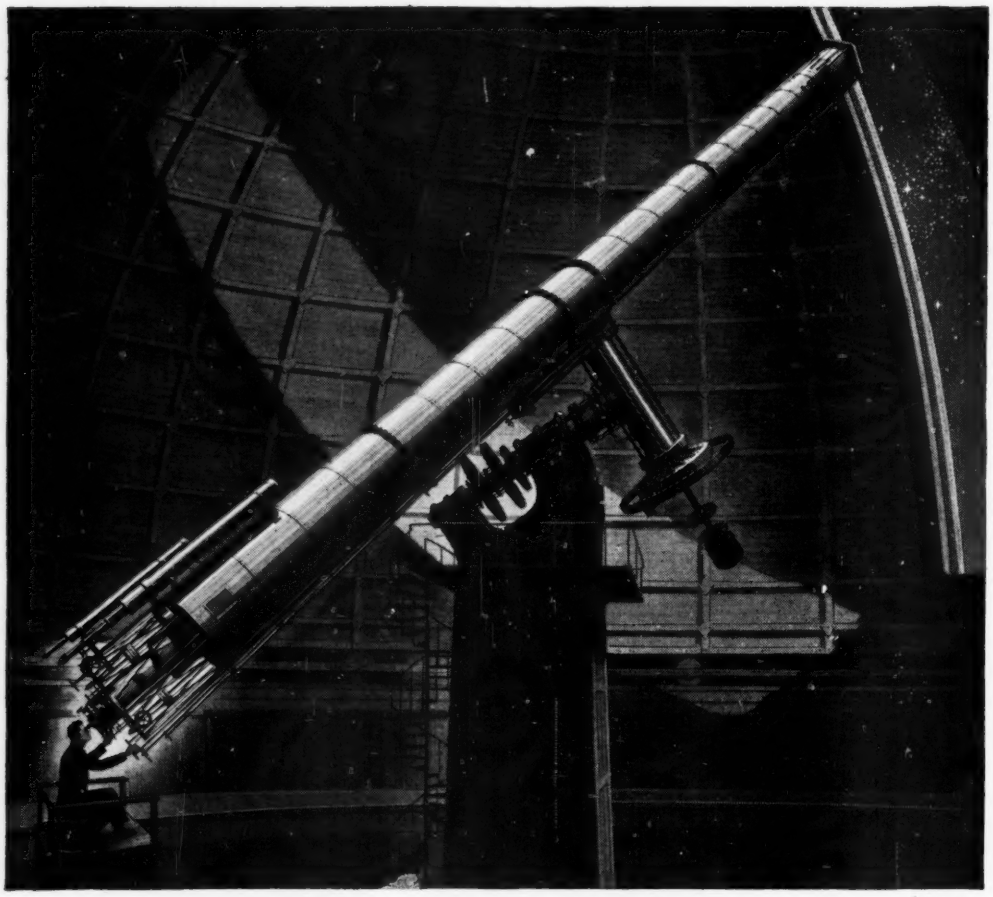

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VOL. 16 JULY, 1944 No. 1

Original Communications

Symposium on Endocrinology of Neoplastic Diseases

SYMPOSIUM ON ENDOCRINOLOGY OF NEOPLASTIC DISEASES

INTRODUCTION

GRAY H. TWOMBLY, M.D., AND GEORGE T. PACK, M.D., NEW YORK, N. Y.

FOR THE individual who is as unfamiliar with the field of endocrinology as the average surgeon is apt to be, the relationship of hormones to cancer is a confusing one. Just the names of the preparations one reads in the current medical journals are apt to give one a hopeless feeling by their multiplicity and mixed etymologies.

Articles appear from time to time describing the production of cancer in experimental animals with hormones, observations which are disturbing to the doctor who wants to use them for his patient. Is he apt to produce a cancer if he treats the oophorectomized woman for her subsequent hot flashes?

Occasionally he is asked to see a patient suffering from a strange set of symptoms which are inexplicable until they are seen to fall into a reasonable pattern which, considered as the effects of too much of one of the hormones, is the result of a functional tumor of one of the endocrine glands. Such tumors are apt to be very rare and most of us are, in consequence, considerably puzzled when we meet with a patient who harbors one.

Recently, with the work of Huggins and co-workers[1] on carcinoma of the prostate, the indication for treating cancer with hormones has become an interesting possibility. The surgeon who has done his best to remove a cancer of the breast by radical mastectomy and then finds himself confronted a few years later with the distressing spectacle of multiple painful bone metastases cannot help but wish that hormone injections could be given which would bring the almost miraculous relief

that is seen in metastatic cancer of the prostate treated by castration or with diethylstilbestrol.

In an attempt to bring together the answers to these questions of what hormones there are, which ones produce cancer in animals and whether they produce cancer in men and women too, what rare symptom complexes are due to functional tumors of the endocrine glands, and whether cancer can be ameliorated or cured by hormones, we have collected the articles in the subsequent symposium. Perhaps the best form of introduction is to present in as simple a form as possible the scientific names of the hormones which have been isolated and characterized in the laboratory, and to indicate in a table the many trade names for the commercial preparations available. (Table I.)

The pituitary gland, the conductor of the glandular orchestra, produces many hormones, all of which as far as we know are proteins. They affect and control the thyroid (thyrotropic hormone), the gonads (gonadotropic hormones), the adrenals (adrenotropic hormones) the pancreas (diabetogenic hormone), growth (growth hormone), lactation (lactogenic hormones), water balance (intermedin), blood pressure and smooth muscle activity (vasopressin), and uterine motility (oxytocin). Two of the anterior pituitary hormones have been obtained in pure form,[2] and the last two, oxytocin and vasopressin from the posterior pituitary, can be separated completely from the anterior pituitary hormone. None of the pituitary hormones has been shown to be important in the etiology of cancer except secondarily (that is, cancer of the breast will not develop in a mouse hypophysectomized in infancy because it has little or no breast tissue).[3] The absence of these hormones seems to slow up the growth of cancer but does not prevent it altogether.[4] The injection of these substances seems to have no effect on the formation or growth of cancer.[5] Perhaps this may be partly due to the formation of antibodies or antihormones[6] when they are injected for they are commonly prepared from the glands of animals other than the species being tested. For instance, sheep and cattle are the source of most of the commercial preparations while rats, mice, and men are the animals bearing cancers which might be used to test their effects. Tumors of the pituitary give weird clinical pictures such as gigantism and acromegaly when the tumor is made up of cells producing growth hormone, Cushing's disease when the cells produce gonadotropic hormone, or infantilism or Simmonds' disease when the tumor presses upon and causes atrophy of these cells. The hormones of the pituitary, then, so far as we know now do not cause or control any form of cancer but may be useful by their effects in diagnosing tumors of that gland.

The same may be said for the thyroid and the adrenal glands. However, both of these organs produce substances which have been isolated in pure form. Thyroxin appears to be the active principle in thyro

globulin and from the adrenal three steroids, corticosterone, 17-hydroxycorticosterone, and desoxycorticosterone, as well as epinephrine from the adrenal medulla, have been isolated. None of these substances has been implicated as yet, either in the formation or treatment of cancer. Hyperthyroidism may result from metastases from a functional tumor of the thyroid.[7] Tumors of the adrenal are apt to give a Cushing syndrome and to produce large quantities of 17-ketosteroids in the urine. The suggestion has been made that this 17-ketosteroid excretion is changed in cancer patients, but just how and why is still under investigation.[8]

The hormones about which the most is known as to both chemical structure and carcinogenicity are those of the ovary and testis. The ovary produces two principal steroids, known as estradiol and progesterone. Estradiol, the structure of which is well established, is broken up and excreted in the urine as organic salts of estrone and estriol. Estradiol has been under suspicion for the last few years as a possible carcinogen because its injection into laboratory animals is followed by the formation of various kinds of carcinoma. In male mice it appears to produce carcinoma of the breast in susceptible strains.[9] It produces Leydig cell tumors of the testis in males of the Strong A strain.[10] It produces a cancer of the cervix in mice,[11] a tumor which does not occur in this species spontaneously. In guinea pigs it causes the formation of fibroma-like nodules on the uterus and in the walls of the gastrointestinal tract.[12] Gardner and his associates[13] have proved recently in rather conclusive fashion that the incidence of lymphosarcoma in mice injected with this material is definitely increased.

The meaning of these observations is obscure. It is probable that in male mice the appearance of cancer of the breast after the injection of large quantities of estrogens for a long time is the expression only of the development of considerable amounts of breast tissue by the hormone in animals bearing a more proximate etiologic factor, a virus found in the milk of susceptible mothers. When no breast tissue is present no cancer can develop. If breast tissue is produced with estrogens, susceptible animals can grow cancer in the tissue so developed.[14] That estrogens are not of themselves carcinogenic but rather that cancer develops secondarily in stimulated tissues is suggested by the fact that the synthetic estrogens seem to work as well as the natural steroids although their chemical structure is entirely dissimilar. The cancer-producing effect is not one that can be reproduced in all species, as evidenced by the failure of estrogenic treatment of guinea pigs and monkeys[15] to cause cancer.

Can estrogens cause cancer in women? Several authors think they have detected such a relationship[16-18] but the cases are rare and isolated and the evidence circumstantial. In these days when few women can complain of menopausal symptoms without receiving large amounts of

TABLE I

ENDOCRINE GLAND	HORMONE	COMMERCIAL PREPARATIONS
Anterior pituitary	Growth	Growth complex or factor Phyone Antuitrin G *Phybentrone Polyansin
	Gonadotropic	Antuitrin gonadotropic Gynantrin Prephysin
	Thyrotropic	Thyrotropic factor
	Lactogenic	Prolactin
	Adrenotropic	Polyansin Antuitrin
	Water balance	Intermedin
Posterior pituitary	Oxytocic	Pitocin Oxytocin
	Pressor	Pitressin Vasopressin
Placenta	Chorionic gonadotropic	A. P. L. Anterior-pituitary-like hormone Antuitrin S *Follutein Anteron Entromone Gestasol *Korotron Pregnyl Pranturon *Synapoidin Antophysin
Probably placenta of the pregnant mare	Pregnant mare's serum —gonadotropin	*Gonadin *Gonadogen
Thyroid	Thyroxin	Thyroxin Thyroid, desiccated *Thyroid extract *Proloid (contains thyroglobulin) *Endothyrin (thyroglobulin)
Adrenal medulla	Epinephrine	Epinephrine hydrochloride Adrenalin Suprarenin Supranephrin Epinine Adrin
Adrenal cortex	Desoxycorticosterone	*Cortate, Percorten } Synthetic *Doca
	Corticosterone	*Adrenal cortex extract *Eschatin *Corticocorbate Cortin *Cortalex } Natural
	17-Hydroxycorticosterone (Compound E)	(None on the market)

TABLE I—CONT'D

ENDOCRINE GLAND	HORMONE	COMMERCIAL PREPARATIONS
Ovary (follicle)	Estradiol	*Dimenformon *Ovocylin *Progynon DH *Progynon B. *Di-ovocylin *Estinyl (Methyl-estradiol)
	Estrone	*Premarin (sodium estrone sulphate) *Theelin
	Estriol	*Emmenin (estriol glycuronide) *Theelol
	Mixtures of the above and related substances derived from urine	*Amniotin *Estrogenic hormones or substances Follacro Menformon Folestrin *Estromone *Urestrin *Estrogens
	(Synthetic estrogens) Diethylstilbestrol	*Stilbestrol *Diethylstilbestrol *Estiobene
	Hexestrol	*Hexestrol *Hexital
Ovary (corpus luteum)	Progesterone	*Progestin Lipolutein Progesterone Progestone *Proluton *Lutocyiin
	Pregneninolone (Anhydro-hydroxy-progesterone) (Has same effect as progesterone but is effective by mouth)	*Progestoral *Pranone *Lutocylol
Testis	Testosterone	*Oreton *Oreton-M *Perandren *Neohombreol *Metandren
Pancreas	Insulin	Insulin Iletin Protamine zinc insulin
Parathyroids	Parathyroid	Parathormone Paroidin

*These compounds have been advertised in the Journal of the American Medical Association; Surgery, Gynecology and Obstetrics; Endocrinology; or Journal of Clinical Endocrinology in the last six months.

estrogenic hormone from their doctors, it would seem that cancer of the breast would occur more frequently after such medication if the drugs were really carcinogenic in the human species. We must conclude then that while estrogens undoubtedly cause certain kinds of cancer in mice, the assumption that they may do so in man must be labeled "not proved" for the present.

Progesterone, the other ovarian hormone, has never been implicated in the production of cancer in men or animals, although some years ago one of us (G. H. T.) observed that animals which had received multiple injections of this material seemed to develop an unexpected number of sarcomas.

Estrogens are elaborated by granulosal cell tumors of the ovary so that their effects, such as premature puberty and menstruation, or postmenopausal bleeding, may betray the presence of the parent tumors.

Estrogens are of particular interest at present because of the marked effects they may have on carcinoma of the prostate. It is really astonishing to see a patient suffering unbearable prolonged pain from metastatic prostatic cancer in bone lose all his pain, regain his appetite, and increase ten or fifteen pounds in weight under the influence of these drugs.[19] Unfortunately the effect is not always prolonged, as in one-third to one-half of the cases it wears off in eight to ten months.

Little can be said of the relationship of testosterone and cancer save that it occasionally causes premature puberty and virility and the infant Hercules type of child when elaborated in excessive quantities by a functional interstitial or Leydig cell type of tumor.[20] The same tumor in an adult causes no noticeable bodily change. Testosterone, by its lack following orchiectomy, is thought to influence the growth of cancer of the prostate. Its administration to patients who have cancer of the breast with bone metastases seems to cause a more rapid absorption of calcium and a consequent rapid growth of tumor,[21] although it does seem to relieve pain perhaps by raising the blood calcium level.

These, then, are the principal hormones elaborated by the body. Their etiologic relationship to cancer is obscure and has been demonstrated only in laboratory animals. While we have no proof that any such connection exists in man between hormones and the formation of cancer, the possibility that such could be the case rests so strongly in the mind that one finds oneself prescribing estrogenic therapy less and less frequently and then only in cases where there is clear indication for its use and preferably in those cases where this use can be controlled in amount and the patient followed and examined from time to time for the possible presence of cancer in the breast or uterus.

It is surprising how many women seem to get along just as well with mild sedatives and suggestion as with potent and possibly cancer-producing hormones.

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TUMORS IN EXPERIMENTAL ANIMALS RECEIVING STEROID HORMONES

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A CARCINOGEN might be defined as any substance or agent, chemical or physical, which when applied under certain conditions is followed by the appearance of tumors which would not have appeared otherwise. Estrogens would be carcinogenic if classified according to this definition. Perhaps they should be so classified—or perhaps the definition should be so modified as not to include the estrogenic chemicals presumably capable of origin within the body. It shall be the purpose of the present review to summarize a portion of the experimental studies on the relation of estrogens to carcinogenesis.[1]

GENERAL OBSERVATIONS

Estrogens were first determined biologically by their capacity to induce growth and cornification of the vaginal mucosa of rats and mice.[2] The other genital tissues of ovariectomized females also showed hyperplasia and hypertrophy following the injection of estrogens[3] which might be characterized superficially as growth-stimulants of specific tissues.[4] In the absence of estrogens or of the ovaries, which are associated with their elaboration, the genital tissues remain infantile or become atrophic. The nature of the process whereby estrogens affect the hypertrophy of the genital tissues is unknown. The absence of trophic manifestations of estrogens on in vitro preparations of genital tissues indicates a lack of direct action on the tissue cells. Vaginal or uterine tissues grown in culture in the presence of estrogen showed no evidence of stimulation.[5] The trophic stimulation in the genital tissues may be elicited by vascular changes in these organs.[6] Their stimulation of all genital tissues except the mammary glands in hypophysectomized animals indicates an independence from the growth-stimulating properties of the hypophysis. Although many attempts have been made to determine how genital growth is affected by estrogens, it can be said with any certainty only that "this is what happened when the animal was subjected to this treatment."

The growth-stimulating activity of ovarian hormones was probably responsible for their original association with the initiation of cancer. Mammary cancer in mice is sex-limited; under normal circumstances males are not affected.[7, 8] Ovariectomy at early ages decreased, and

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reproductive activity increased, the incidence of mammary tumors in mice of certain inbred lines but not of other lines.[8-11] Subsequently, strains of mice were developed which showed, within each strain, consistent, but among the different strains, varying incidences of mammary tumors.[12, 13] Leo Loeb probably first expressed the influence of hormonal factors in cancer in experimental animals by the formula: Genetic or inherited factors plus internal secretions give mammary cancer.

An almost universal characteristic of female reproductive phenomena is its cyclic or rhythmic nature. Periods of proliferation and hypertrophy alternate with periods of atrophy or regression during the different phases of the estrous or menstrual cycles. This generalization might afford a mechanism protecting against too great or prolonged trophic stimulation. The genital tissues were at least capable of responding when periodically stimulated. Under experimental conditions could the stimulation be more or less indefinitely prolonged? What would be the character of the response under such conditions? Finally, would any relation exist between an accentuated or prolonged trophic stimulation of specific tissues and the assumption of the quality of unrestricted or malignant growth by these tissues? Attempts to obtain answers to these questions undoubtedly prompted the experiments to be summarized.

Investigations in which mice have been used have contributed most extensively to the knowledge of hormonal factors in carcinogenesis. Geneticists observed many years ago that certain inbred lines or groups of mice showed a high incidence of spontaneous mammary adenocarcinoma in females. Further inbreeding and selection has resulted in the existence of several inbred strains in which mammary tumors have appeared for many successive generations.[13] Among mice of other equally or nearly equally inbred strains, mammary tumors appear with less frequency, and in still others they rarely occur. It is but natural that such well-controlled material should be used in a study of factors influencing the incidence of cancer.

Ovariectomy and Mammary Cancer.—The ovaries have been associated with the development of the mammary glands for many years.[14] The possible relation of these glands to mammary cancer was investigated by their removal or by their transplantation into males of the same strain.[11] Ovariectomy of mice at ages of 3 to 5 months largely inhibited the occurrence of mammary tumors. The incidence of such tumors was greater in mice ovariectomized when 5 to 7 months old and was not altered in mice ovariectomized at later ages.[7] These observations have been confirmed in their essential points by other investigators,[10, 11] although the ages at which tumors did not appear subsequent to castration varied.

An exception to the usual observation that ovariectomy at an early age prevents the appearance of mammary tumors in mice has recently

been reported, but it need not alter the inference that the removal or reduction of ovarian hormones reduces the incidence of mammary cancer. Mice from two strains, ovariectomized while very young, developed mammary tumors many months later.[15] These mice showed either a marked hypertrophy or tumors of the adrenal glands, and their accessory genital organs showed evidence of estrogenic stimulation. Similar observations were made on hybrid mice ovariectomized when about 2 months old.[16] Male mice, which normally are not subject to mammary tumors, showed such lesions when they were castrated at a very early age.[15d] It might be concluded that the disturbance of the endocrine system created by a gonadal deficiency results in the alteration of adrenal function and morphology and frequently the acquisition of adrenal adenomas or even carcinomas. These altered adrenal glands compensate in part for the removed ovaries, the mammary glands are stimulated, and mammary tumors appear. In my opinion these experiments are uniquely significant in that they demonstrate the nice balance which must exist in the normal animal and how prolonged alteration of this balance may slowly alter other functions materializing in profound changes which may in some ways even overcompensate for the initial deficiency. Similar adrenal lesions have been described in castrated guinea pigs, although in this species the hosts were masculinized.[17]

Ovarian Grafts and Mammary Tumors.—The second surgical approach to the problem of ovarian hormones in mammary carcinogenesis has likewise given equivocal results. The transplantation of ovaries into male mice of the same strain led to the appearance of mammary tumors in some of the recipients.[11, 18] The incidence of such tumors was not high but approached that of virgin females of the same strain.[11] Male mice of other strains in which the females are susceptible to mammary tumors did not acquire mammary tumors after ovaries had been grafted into them.[19, 20] The grafting of a female animal to a male (parabiosis) did not result in mammary tumors in the male.[21] The later experiments create a more complicated endocrine relationship than the transplantation of ovaries. Mice which had ovarian tumors subsequent to x-irradiation showed a much higher incidence of mammary tumors than mice in which ovarian neoplasia did not occur.[22]

Other Methods of Investigation of Ovarian-Mammary Tumor Problem.—Two more or less direct methods of experimentation were afforded at this point to investigate how the ovary or its hormones might be related to mammary carcinogenesis. In the first place the possibility of an excessive production of ovarian hormones in mice of the tumor-susceptible strains or lines could be investigated. In the second place additional or excessive amounts of hormones could be added to mice of the different strains and the incidence of tumors observed.

Studies on Estrogen Levels in Mice of Strains Which Differ in Susceptibility to Mammary Cancer.—The hormonal environment to which mammalian tissues are exposed might be estimated to some extent by study-

ing the comparative reproductive capacities of animals of tumor-susceptible or resistant groups, by comparing the mammary glands, or vaginal estrous cycles. Direct estimation of the elimination of sex hormones in animals of different strains can also be made.

In some instances it has been possible to associate evidence of excessively prolonged or frequent estrous periods with the tendency to develop mammary tumors.[23] When the previously stated observations were extended to include mice of several strains, the correlation no longer existed.[24] Mice of different strains had estrous cycles which tended to differ from each other in the length and frequency of estrus, but this was not necessarily related to the tendency to acquire mammary tumors.[25] No differences were detected in the estrous rhythm, age of onset, or age of cessation of estrus of other low- and high-tumor strains.[26]

The mammary glands might also afford some indication of the hormonal environment. Several investigators have noted differences in the mammary glands which they associated with the tendency for certain strains to acquire mammary cancer.[27] These differences in morphology involved essentially the presence of localized areas of alveolar tissue described by Haaland.[28] When the glands of young[29] or old mice[30] of ten and six strains, respectively, were compared, the differences in general mammary morphology could not be associated with the tendency to acquire tumors. Strain differences did exist, however.[29] The morphologic aspects that could be associated with the tendency to acquire mammary tumors involved the specific proliferation of localized nodules of mammary tissue in otherwise atrophic glands. "The presence of localized proliferation of mammary tissue in animals from strains susceptible to mammary cancer, while the rest of the gland was in a state of regression or inactivity, indicates that various areas of the gland show different growth responses in the presence of a supposedly uniform environment. The importance of localized nodular areas in otherwise involuted glands is indicated by their frequent occurrence in strains liable to progressive adenomatous and malignant change. The early appearance of hyperplastic nodules, their numbers, and their variable structure suggest a progressive series of abnormal changes in the mammary parenchyma leading to malignancy."[30] The extent of involution or proliferation of the internodular areas was not related to mammary tumor susceptibility. Recently one group of investigators who observed a greater abundance of alveolar elements in the glands of a high- (dba) than in a low-tumor strain of mice noted that the tendency was transmitted by the female in hybridization.[31] "There is a strong positive correlation between the architecture of the mammary glands in different types of mice with regard to the degree of its disposition for cancer." Other morphologic features of the mammary glands were of intermediate prominence in the hybrids irrespective of the maternal parent. Similar observations have been made in another laboratory when the mammary

glands of mice of the dba strain were compared with mice of the C_{57} strain.[32] Experiments involving reciprocal hybridization of other high- and low-tumor strains failed to reveal significant differences in the general mammary morphology, although the localized hyperplastic nodules were largely transmitted by the female parent.[33] The observations on the comparative morphology of the mammary glands of mice of strains showing different susceptibilities to spontaneous mammary tumors are not in agreement. The writer's observations indicate no relation of general mammary structure to tumor susceptibility as contrasted to the observations of two other investigators.

Reproductive histories have been recorded for mice of several inbred strains presumably maintained under rather uniform conditions.[34] Striking strain differences have not been revealed which could be associated with the tendency to acquire cancer. In some strains virgin female mice frequently acquire mammary tumors[35] and frequent pregnancies may increase the incidence in mice of low-tumor strains.[36]

Recently studies have been conducted on the urinary elimination of estrogenic substances from mice of the high- and low-tumor strains[37] and also of the capacity of hepatic tissues of these mice to inactivate estradiol.[38] These studies have not revealed significant differences that could be associated with susceptibility to mammary cancer.

Mice of several inbred strains showed some variation in their response to minimal amounts of estrogen. One investigator attached little significance to the slightly greater response of the low-tumor CBA mice than of the high-tumor A mice.[26] Another group compared the vaginal response of C_{57} and dba mice and found that the latter required nearly three times as much hormone as the low-tumor mice and that F_1 hybrids needed intermediate amounts,[39] but resembled the low-tumor C_{57} strain more closely than the dba strain. The females which had genital organs least susceptible to estrogens were considered to produce the largest amounts of hormone under normal conditions. The ovaries of mice of the dba strain were larger than those of C_{57} mice.[32] The mice of one inbred strain (CBA) showed less uniformity of response of the vaginal epithelium to estrogens than market mice of variable origin.[40]

These observations might be summarized as follows: (1) The strain-limited tendency of mice to acquire mammary tumors cannot be associated consistently with evidences of an abnormal intrinsic hormonal environment. (2) The mammary glands of susceptible mice may or may not be identified from those of low-tumor strains by their general morphologic characteristics but they do show localized areas of hyperplastic epithelial tissues rarely found in the glands of mice of low-tumor strains. The latter condition can be associated with the tendency for mammary tumors to appear and, as will be discussed later, may represent early stages in the assumption of malignancy.

Rats and rabbits of some strains or groups acquire benign or malignant mammary or uterine tumors. These tumors appear among animals

showing evidences of an altered reproductive capacity or presenting a glandular syndrome. The benign mammary tumors in rats of the Albany strain occur in animals showing a high incidence of sterility, irregularities of estrous cycles, and a tendency to have hypophyseal adenomas.[41]

The mammary[42] and uterine tumors[43] in rabbits occurred in animals which at some time had toxemia of pregnancy[44] and had acquired a persistent hepatic damage. Associated with this condition were degenerative lesions in the adrenal cortices and hypophyseal hypertrophy.[42] The genital tissues showed prolonged periods of general hyperplasia, progressing to benign neoplasia and finally malignant tumors.

Studies of these types are of great interest. In some ways they contribute much more than experiments in which one or more sex hormones are administered. Such observations must be made in many animals so that the possibility of their etiologic relationship or concomitant nature can be evaluated. The rats and rabbits mentioned are representatives of selected populations.

Experimental Alteration of Estrous Cycles.—The endocrine system may be profoundly disturbed by experimental manipulation. The removal of the greater part of the ovaries of guinea pigs has resulted in a disturbance of the gonad-hypophyseal relationship and excessive uterine hyperplasia in guinea pigs.[45] The partial destruction of the ovaries by x-irradiation also resulted in a cessation of the estrous cycles and evidence of excessive ovarian activity.[46] The ovaries of the guinea pigs were largely composed of interstitial tissue. The estrous cycles of rats[47] and mice[48] may be permanently altered if testes of littermates are grafted into them shortly after birth. The mice showed a marked hypertrophy of their genital tracts and prolonged periods of estrus. The reproductive activity of rats may be profoundly and permanently altered by brief treatment with estrogens or androgens before the fifteenth day after birth.[49] Some of the animals had uterine lesions similar to those attributed to chronic estrogenic treatment.[49b]

These experimentally produced "syndromes" probably all result from an altered endocrine balance which destroys the capacity for the rhythmic characteristics of female reproductive phenomena. The amount of estrogenic substance effective within the body is probably not excessive in amount but the tissues are stimulated continuously and are not permitted to regress.

Administration of Estrogenic Hormones and Mammary Tumors.—The earlier experiments on the administration of estrogens upon the appearance of mammary cancer in experimental animals did not reveal any detectable carcinogenic effect. Estrogenic preparations were not concentrated.[10, 50] Moderate or large amounts of hormone could not be administered over prolonged periods. A cystic and adenomatous condition of the mammary glands was observed which was compared with Reclus disease.[50]

Lacassagne, in 1932, first reported a carcinogenic effect of estrogens on the mammary glands. Multiparous female mice of one of his strains frequently showed mammary tumors. Male mice never acquired such tumors. The injection of folliculin benzoate in oily solution into male mice, starting shortly after their birth and continued at weekly intervals, resulted in mammary tumors. The tumors resembled those which appeared among the females. Mammary tumors thus appeared in animals in which they would not have appeared had estrogens not been administered.

These experiments might be interpreted in either of two ways: (1) Estrogens directly elicit abnormal or malignant growth, or (2) estrogens merely initiate mammary proliferation so that tissue is available to undergo malignant transformation.

Lacassagne[51] immediately set about checking these interpretations. Mice from one strain showing a low incidence of mammary tumors showed a higher incidence of such tumors after the injection of estrogens. Another strain of mice in which mammary tumors rarely appeared showed no tumors after the injection of estrogen.

Lacassagne's observations have been confirmed and extended by many investigators. Male mice from strains in which the females develop mammary cancers acquire such tumors after the injection of estrogens.[52] In some strains the tumors occur at earlier ages than in the untreated mice. The incidence of mammary tumors was not as high in estrogen-treated mice of some other high-tumor strains or hybrid groups as in multiparous females of the same strains.[53] Only in a very few instances have mammary tumors appeared among estrogen-treated inbred mice of low-tumor strains,[54] or stock mice[55] in higher incidences than among the multiparous controls. The incidence of tumors was not exceptionally high in these latter experiments.

The administration of estrogens of widely different chemical structures such as estrone, estradiol, equilin, equilenin,[56] and their benzoates or propionates, stilbestrol,[57] and triphenylethylene[58] affect similar mammary changes when administered in amounts that are physiologically comparable. This generalization is apparently true for both the capacity to elicit the normal proliferation of the mammary tissue[59] as well as any association with abnormal or malignant proliferation. The estrogenic hormones apparently do not have any chemical specificity for mammary carcinogenesis that cannot be associated with their estrus-producing capacity.

The estrus-producing hormones in mice act only in combination with factors or "influences" transmitted from parents or maternal parent to offspring for mammary carcinogenesis. The incidence of mammary tumors among mice from strains showing a high or moderate incidence of cancer is usually increased or tumors appear earlier in the estrogen-treated animals than in the respective controls. Mice from strains in

which spontaneous mammary tumors rarely appear do not acquire or rarely acquire such tumors when estrogens are administered. Hybrid male mice obtained by crossing mammary tumor-susceptible and low-mammary tumor strains, when treated with estrogens, have an incidence of cancer approaching that of the maternal strain.[53c] A similar tendency for the appearance of cancer exists among untreated multiparous females of comparable origins.[60] The tendency to acquire mammary tumors was transmitted largely through the ingestion of milk during the nursing period.[61] Young mice born from tumor-susceptible mothers but fostered on low-tumor females did not acquire tumors after pellets of estrone or estradiol benzoate had been implanted.[62] The young of low-tumor mothers which were fostered on high-tumor females acquired mammary tumors when estrogens were administered in one experiment[63] but not in another.[62] These observations indicate that estrogens are no more than a contributing factor in the initiation of mammary neoplasia. Although in male mice the estrogens result in some development of the mammary glands, in the absence of which mammary tumors do not appear, other factors must also exist in these animals before tumors arise.

This conclusion is supported by the observation that mammary cancers appear in male mice from tumor-susceptible strains at six to sixteen months after the last injection of estrogen.[64] The period of treatment of such animals must be sufficiently prolonged to assure considerable mammary development (eight to twelve weeks).[65] The incidence of tumors in such animals is usually considerably lower than in mice continually treated with estrogen.

The amounts of estrogenic hormones injected have also been studied in relation to their mammary carcinogenic actions. Amounts large enough to result in optimal growth of the mammary ducts do not appear as effective in mammary carcinogenesis as larger amounts.[66] Very large amounts were not only quite toxic as far as the animals were concerned, but inhibited mammary proliferation and the incidence of mammary tumors was low.[67] Within limits, the larger the amount of estrogen administered the earlier mammary tumors appeared.[68]

Mammary Tumors in Estrogen-Treated Animals of Other Species.—Mammary lesions of several types have been observed in rats given estrogens. All of six castrated female rats which had received 30 μg. of estrone daily for 331 days or more, showed multiple mammary cysts and one had an adenofibroma.[69] Mammary cancer appeared in other treated rats.[70] Other investigators observed cyst formation and stunted growth of the glands in animals similarly treated.[71]

A very high incidence of mammary tumors occurred among rats given pellets or both pellets and injections of estrogens.[72] In some groups most of the animals developed tumors. Among 555 rats treated with estrogens, 202 mammary cancers appeared.[73] Two animals showed

multiple metastases to the lungs and lymph nodes. The larger the dose of hormone the earlier the tumors appeared.[72] Untreated rats of the same colony did not develop mammary tumors.

Approximately 60 per cent of the rats which survived 7 months or more and which had pellets of estrone implanted on the fifth to seventh days of life acquired mammary tumors after 226 or more days. The tumors were usually multiple and grow slowly although they were extremely hyperplasic.[74]

Metastatic growth was found in the lungs of one rat bearing a mammary tumor.[75] These tumors failed to grow following transplantation into other animals or into other sites in the same animal unless the hosts had pellets of estrone implanted. The tumors regressed after removal of the estrogen and after the injection of progesterone.

Experiments With Monkeys.—The breasts of young male monkeys grew to morphologically complete tubulo-alveolar glands when estrogen was administered.[76] Prolonged periods of treatment with large amounts of estrogen resulted in "stunted" mammary glands.[67] Other observations on monkeys given even larger amounts of estrogen, likewise, failed to reveal malignant growth although metaplastic islands appeared in some glands.[77] Localized hyperplastic or secreting areas of mammary tissue were found in ovariectomized monkeys.[78]

Other Species.—Although large amounts of estrogens have been administered to animals of several species, especially rabbits and dogs, mammary tumors have not been reported.

Mammary Changes Elicited in Animals Receiving Estrogens.—It has been stated that the mammary glands of adult and old mice of the tumor-susceptible strains usually showed localized hyperplastic nodules.[28, 30, 33] These nodules varied greatly in structure from small lobules of alveoli, sometimes secreting, to small hyperplastic adenomas or even small adenocarcinomas histologically similar to the larger tumors.

Similar morphologic changes occurred in the glands of estrogen-treated male or female mice of the same strains.[33, 79] Some of the lesions have been compared with the microscopic appearance of nonmalignant hyperplastic lesions in man.[32, 50, 51b, 52, 80] In mice these localized hyperplastic lesions can be said to be precancerous in the sense that they have been so uniformly found in mice with the tendency to acquire mammary neoplasia. The tissues composing these nodules must respond to other stimuli, which elicit reactions in the normal mammary tissues. Many of these nodules are found in stages of regression indicating that many are not autonomous. Some of these nodules apparently go through several stages of atypical growth terminating in adenocarcinoma.[79b] Although mammary cancer may seem to be a local disease, the wide distribution of the "precancerous" lesions indicates that all of the mammary tissue or that many areas of mammary tissue may be involved simultaneously.

Another type of morphologic change occurring in the mammary glands of estrogen-treated mice is found both in the low- and high-tumor mice.[32, 33c, 79, 80] The larger ducts and some of the smaller ducts and alveoli become distended with a concretion-like secretion. The ductal distention may be extreme. The epithelium of the surrounding ducts may be absent or epithelial cells may surround the secretion. A moderate increase in the surrounding fibrous connective tissue may occur. The effects of age and estrogen treatment on the mammary connective tissue have been studied extensively.[32, 33, 80, 81]

Summary of Effects of Estrogens on Mammary Carcinogenesis.—Several phases of the investigations just reviewed indicate that estrogens may have little direct effect upon mammary carcinogenesis in mice. These might be summarized briefly as follows: (1) The relative physiologic activity of the different estrogens is associated with the tendency for their injection to result in the appearance of tumors in suitable animals. (2) Hereditary or transmitted factors dominate the appearance of tumors in estrogen-treated animals. (3) In suitable animals mammary tumors can appear long after the last exposure to injected estrogens. (4) To these may be added the fact that in mice estrogens have very little mammary stimulating activity in the absence of the pituitary gland, as will be discussed later.

On the other hand some evidence indicates carcinogenic effect of estrogens: (1) Without mammary glands of at least moderate size which develop when estrogens are administered to intact mice, no mammary tumors appear. (2) Amounts of estrogen adequate for mammary proliferation are not necessarily optimal for mammary cancer.

The mechanism whereby mammary cancer appears when estrogens are injected in suitable animals is not known. It has been stated that "estrogenic hormones do not cause cancer formation because they give origin to a larger amount of tissue, which thus would be a more favorable field of attack for the unknown agent representing the real cause of the cancerous transformations. But the hormone leads to the formation of new tissue because it stimulates the glands and because it stimulates the gland tissue it causes the cancer formation. Both increase in the amount of tissue and cancerous transformation are therefore the result of the same condition, they are coordinated and not subordinated phenomena."[81a] This might represent one extreme viewpoint.

There is also sufficient experimental evidence to suggest the following theory. Mammary growth occurs in the animals with functional pituitary glands when estrogens are injected. In the presence of some other factor or agent and estrogen, localized proliferative or precancerous nodules of breast tissue appear in glands in which other areas may be refractory to estrogens. The appearance of mammary adenocarcinoma in and among the localized nodules can occur subsequently in the absence of estrogens. Many of these nodules are re-

versible, attaining certain stages of atypical structure and regressing. If the active growth-stimulating phase were responsible for the tumors the neoplasia might be expected to occur early. Instead, cancer does not appear until the greater part of the glands have become refractory to estrogens. Estrogens may therefore contribute to the premalignant phases of tissue change or to the environment in which these changes occur.

Factors Involved in Mammary Proliferation.—A number of years ago it was considered that estrogens stimulated mammary growth but the absence of, or limited mammary growth in estrogen-treated hypophysectomized animals altered this interpretation.[14] Several theories have been proposed: (1) Estrogens may act upon the pituitary causing a release of a mammotropin.[82] (2) The mammary glands may be incapable of response to estrogen because of the other deficiencies existing in hypophysectomized animals.[83] When progesterone, desoxycorticosterone, or prolactin were administered with estrogen, mammary growth occurred.[83a, b] In intact animals the cutaneous application of small amounts of estrogen induced mammary growth only in the subjacent glands.[83d, e] During the latter part of pregnancy the hypophysis is not necessary for mammary growth.[14]

In intact animals of some species estrogen alone will result in complete mammary growth,[76] but in others progesterone is required for the development of the alveoli. When the corpora lutea are active, as during pregnancy or pseudopregnancy, alveoli form.[85, 86] Progesterone may induce some alveolar development when administered with estrogens.[85]

Influence of Androgens and Other Steroid Hormones When Administered Alone or With Estrogens. Mammary growth occurred in mice receiving several different steroid hormones such as testosterone, androsterone, progesterone, and desoxycorticosterone when they are administered in large amounts.[87] Two of three mice of a tumor-susceptible strain which received 100 μg. of estrone and 0.5 to 1.0 m.g. of testosterone on alternate weeks developed mammary tumors after several months.[88] Also, two females of the same strain given testosterone (0.5 to 1.0 mg. weekly) from birth acquired mammary tumors. Similar results were obtained with larger numbers of mice and with other strains.[89]

Testosterone propionate, when administered in very large amounts to uniparous C_3H mice more than 4 months of age either greatly reduced the incidence or delayed the appearance of mammary tumors.[90] Smaller amounts of testosterone (1 mg. weekly) reduced the incidence of tumors expected when the injections were started early in life, but did not alter the appearance of tumors in multiparous animals.[91] Experiments undertaken in another laboratory also indicate that testosterone propionate in very large amounts will decrease the incidence of mammary tumors in estrogen-treated animals.[65]

Desoxycorticosterone, 2 to 4 mg. per week, induced mammary growth in male mice.[87] One milligram or less per week did not lead to mammary cancer in male mice of the C_3H strain or alter the incidence of tumors in female mice.[92]

Progesterone, when administered in large amounts, results in mammary growth.[93] When administered with estrogen (50 to 100 μg. estrone and 200 μg. progesterone on alternate weeks) the incidence of mammary tumors did not differ from that expected after estrone alone.[88, 89]

Although these hormones to some extent modify some of the reactions elicited by estrogens, they have either little or no capacity to reduce or alter the incidence of malignant mammary growth unless given in very large doses.

Hyperplasias, Tumors, and Carcinomas of the Uteri of Experimental Animals.—Atypical and hyperplastic uterine conditions, particularly those classified as glandular cystic hyperplasias and fibroids, may follow abnormal ovarian function.[94] The injection of estrogen into spayed or intact female monkeys, in some instances associated with cervical trauma, led to hyperplasia and metaplasia of the cervical glands.[95] These lesions did not grow progressively and would revert when progesterone was injected.[96] The uteri tended to become refractory after prolonged treatment.[77]

Atypical hyperplastic or metaplastic lesions of the uterine fibromuscular tissue or of the epithelial tissues of both the uterus and uterine cervix have been referred to. The experimental work undertaken will be divided on that basis for presentation.

Fibromuscular Reactions.—Fibromyomatous overgrowths appeared in the subserosa or myometrium of guinea pigs receiving estrogens over prolonged periods. Some of the tumors involved the mucosa, and excessive uterine hemorrhage occurred.[97] Similar lesions have been noted by other investigators.[98, 99]

Fibromyomatous tumors not only occurred on the uterus but also throughout the abdominal cavity.[99] These tumors tended to occur especially in relation to the mesenteries and peritoneum of the spleen and stomach. They were histologically malignant in that they occasionally invaded the pancreas, liver, other viscera, and the body wall.[100] Their site of origin is not definitely known but the peritoneal mesothelium has shown the earliest proliferative lesions.[100, 101] The tumoral reaction occurred in both males and females, although more readily in the latter.[102] A large series of normally occurring estrogens and their esters, as well as stilbestrol and hexesterol, elicited the tumorigenic reaction in guinea pigs. The simultaneous administration of progesterone, desoxycorticosterone, and testosterone prevented the development of the tumors.[103] These tumors are not autonomous growths in that they regress when estrogenic treatment is discontinued. The term tumorigenesis was ap-

plied to the process rather than carcinogenesis.[104] As far as is known similar tumors have not been described in estrogen-treated animals of other species.

Benign and malignant epithelial tumors of the uteri of experimental animals rarely appear even after the injection of estrogens. Glandular overgrowths or glandular cystic hyperplasia may appear after the injection of estrogens in rabbits[105] and guinea pigs.[97, 105c] The uteri of estrogen-treated rabbits undergo progressive aseptic infarct necrosis.[105d] Septic inflammatory reactions (pyometra), epithelial metaplasia, and glandular cystic hyperplasia have been frequently described in estrogen-treated rats and mice.[106] It is possible that the uterine metaplasia is secondary to the septic condition which, in mice, occurs following the injection of estrogen.[107] Glandular cystic hyperplasia has been observed in estrogen-treated monkeys,[108] although not consistently.[77, 95c, 109] Lacassagne[110] described a small uterine carcinoma in an estrogen-treated mouse.

Malignant epithelial growths of the uterine cervices of estrogen-treated mice have occurred frequently, and atypical hyperplastic and locally invasive lesions in this area have been studied extensively. These observations are probably of further significance because carcinomas of the uterine cervices of untreated mice occur rarely.[111]

Three of twenty-seven mice which had received estrogen and cutaneous applications of 1:2:5:6-dibenzanthracene for six to ten months had cervical carcinomas.[112] The largest tumor had invaded the bladder and other pelvic tissues.[55b] At the same time a carcinoma-like overgrowth was described in a mouse which had received estrogen (theelol for eighteen and theelin for six months) for over twenty-four months.[113] This tumor had invaded the muscularis and serosa. Similar lesions were observed among other mice injected with estrone or estradiol benzoate.[52g] Twenty-six of 235 estrogen-treated mice showed either precancerous or cancerlike lesions of the uterine cervix or upper vagina.[114] The cervices of 128 untreated mice were also studied microscopically. Epithelial irregularities of the upper vaginas and cervices of both treated and control groups appeared more frequently with advancing age. The more advanced lesions occurred in the estrogen-treated mice. The strain of the mice or the tendency to develop mammary tumors did not alter the tumorous response of the cervix.

One of nineteen cervical lesions was observed in a living mouse which had received estradiol benzoate for 319 days, a total of 10,500 I.U.[115] When this mouse was killed the tumor was transplanted into other mice of the same strain and it grew progressively. The squamous-celled carcinoma had apparently arisen from the cervix but involved the entire pelvis and the lumbar nodes. Three carcinomas and twenty-four invasive epithelial lesions appeared among 134 estrogen-treated mice of four different inbred strains.[116] Four of eight mice which had received

estradiol benzoate and testosterone propionate simultaneously had cervical lesions, of which two were considered malignant.

A high incidence of invasive lesions of the cervical epithelium arose in estrogen-treated mice from groups which tolerated estrogens for extended periods.[117] Over 50 per cent of the forty-four mice had cervical lesions after they had received 16.6 μg. of estradiol benzoate weekly for one year or more.

Some investigators have not observed cervical tumors in estrogen-treated mice.[53c]

Summary of Effects of Estrogens on Invasive Epithelial Lesions of the Cervix.—Estrogens stimulate growth of the female genital tissues but the cervical cancers which appear after prolonged estrogenic treatment arise as local proliferative lesions in otherwise relatively quiescent cervical areas.[114, 116, 118] There is no evidence that inherited or transmitted factors or agents are involved in this neoplastic reaction. The tendency to acquire cervical tumors is not associated with the tendency to acquire mammary tumors. Why the neoplastic response of the mouse's genital tract is limited to the cervix and vaginal fornix is not known. The external os has been most frequently involved in animals with small lesions and presumably the larger growths arose at this location.

The mouse's genital tract with its bicornuate uterus and aglandular cervix differs greatly from that of primates.

Tumors of the Testes in Estrogen-Treated Mice.—Estrogenic hormones when administered to males usually resulted in a decrease in the size of the testes. The seminiferous epithelium and the interstitial elements were both reduced and evidence of androgenic activity decreased or disappeared.[119] The gonadotropic hormone in the hypophyses of such animals was decreased.[120]

The administration of estrogens (equilin and estradiol) for prolonged periods resulted in a hypertrophy of and an increased number of glandular interstitial cells in mice of unknown genetic origin.[59, 121] In another laboratory this marked hypertrophy of the interstitial cells was limited to the mice of one inbred strain, which had received either estradiol benzoate or equilin benzoate.[122] Three of the mice receiving equilin benzoate had large circumscribed areas of interstitial cells in their testes. These experiments "indicate that some estrogenic chemicals act upon the pituitary, stimulating the formation of increased amounts of hormone (luteinizing hormone or interstitial cell stimulating hormone) capable of transforming the interstitial cells."[122] Similar nodules were not found in the testes of mice of four other strains similarly treated. Burrows described an estrogen-treated mouse with an adenomatous interstitial cell tumor which showed little of the changes of the seminal vesicles and prostate, usually associated with such estrogen treatment.[123] He assumed that the mouse had become refractory to the estrogen.

More recently testicular tumors have been reported in mice of the A strain which have received either triphenylethylene,[124] estradiol benzoate, or stilbestrol.[125] These tumors, although composed chiefly of large glandular cells, invaded the tunica albuginea and surrounding tissues and the lymph nodes of the lumbar and perirenal regions. Mice of a different strain (C) in another laboratory showed testicular tumors when exposed to estrogens for long periods.[126] Testicular tumors did not appear among animals from two other strains given triphenylethylene or estradiol dipropionate.[124]

The sequence of morphologic changes in the testes of estrogen-treated mice of the A strain has indicated that progressive phases of atypical cells appear, and that several types (generations) of cells may contribute to the same or different tumors.[127a] Testicular tumors have also appeared in mice of the JK strain, which have received triphenylethylene.[127b]

The interstitial cell tumors, even those which have extended to the lymph nodes, apparently elaborate an androgenic substance.[125, 127] The seminal vesicles and prostates of animals with such tumors may be enlarged and filled with secretion in spite of the simultaneous injection of estrogens. The tumors grew when transplanted subcutaneously into other mice of the same strain when estrogens were injected into the hosts.[127]

Nodules of interstitial cells have appeared near the hilus of the testes of mice of the A strain that have received injections of pregnant mare serum for long periods. One testicular tumor appeared in a mouse treated first with estrogen and then with Gonadin (a gonadotropic hormone from mare's serum).[128] A marked hypertrophy and hyperplasia of the interstitial cells occurred in mice treated with prolactin.[129]

Testicular tumors have not been described in estrogen-treated animals of other species. In mice they, like the mammary tumors, appear to be strain-limited. Unlike mammary neoplasms the tendency for tumors of the testes to appear in the hybrid young is transmitted by both males and females.[65] It is interesting that the testicular as well as the mammary and cervical tumors appear after prolonged stimulation and after the tissues have failed to respond in the usual manner or have regressed.

Male Accessary Glands.—A great many studies have been undertaken in which lesions of a hypertrophic or metaplastic type have been observed in the prostates and seminal vessels of rats and mice. The simultaneous administration of androgen largely counteracted the effect of the estrogens. Tumors of these tissues have not occurred. The literature has been previously reviewed[1a, 3] and will not be repeated here.

The experiments in which dogs and monkeys have been used, although they have not led to the malignant growths, are of greater interest. Daily injection of 800 to 2,000 I. U. of estrone for five and one-half to seven weeks resulted in an eightfold increase in the size of the prostates

of young dogs.[130] Dogs with "feminizing" testicular tumors had large prostates.[131] The enlarged prostates contained excessive amounts of fibromuscular stroma and glands distended with or lined by a metaplastic stratified squamous epithelium. The extent of epithelial metaplasia was inversely related to the fibromuscular hypertrophy. Smaller doses of estrogen (stilbestrol) reduced the size of the functional or hyperplastic prostate while larger doses enlarged it.[132] The hyperplastic prostates decreased in size following castration.

The injection of estrone caused a marked hypertrophy of the seminal vesicles of immature male monkeys. The epithelium of the prostatic utricle, colliculus seminalis, and cavernous urethra became thickly stratified.[133] The prostatic enlargement was largely attributable to an increase of the utricular tissue.

Pituitary Tumors Among Estrogen-Treated Animals.—A sex difference in the size and histology of the hypophysis has been described in several species.[135] Among experimental animals the estrogenic hormones markedly alter the size and structure of the hypophyses of rats and some mice.[136]

Almost simultaneously three different investigators described marked hypophyseal hypertrophy or adenomatous proliferation of the hypophyses in estrogen-treated rats or mice.[137] The chromophobic cells constituted the greater part of the anterior lobes of the enlarged glands of these animals.

Among mice spontaneous tumors of the hypophyses rarely occur.[138] One chromophobic adenoma appeared in a mouse with bilateral ovarian granulosa cell tumors.[139] Marked hypophyseal enlargement rarely occurred among estrogen-treated stock mice (1 in 679),[140] or among estrogen-treated mice of three inbred strains.[52g] The tumorous transformation of the hypophyses did not occur in estrogen-treated mice of all strains[56] and could not be associated with the tendency of the different strains to acquire mammary tumors.[141] Hypophyseal tumors appeared frequently only among estrogen-treated mice of one low-mammary tumor strain in one laboratory and not among mice of six other strains similarly treated.[142] Both male and female mice of this strain transmitted the tendency to develop pituitary tumors to their offspring.[53c] The tumors appeared more frequently and at an earlier age in males than in females and attained sufficient size to force the cranial sutures and alter the shape of the head.

All of the pituitary tumors in mice have consisted of chromophobic cells. The smaller tumors usually resemble generalized hyperplasias of the chromophobes. The larger tumors, although not circumscribed, were made up of more hyperplastic cords of chromophobic cells and were probably adenomas. They may be transplanted to other mice of the same strain.[65] Some of the tumors may be a deep red color and contain large sinusoids or even hemorrhagic areas.

Large hypophyseal tumors also appear in rats receiving large amounts of estrogen.[143] The vascular tumors were composed largely of chromophobic cells with large Golgi nets. The few chromophilic cells were largely degranulated.[144] Pituitary tumors have been observed in castrated male rats bearing ovarian grafts.[145]

Small hypophyseal tumors have been observed in a number of untreated rats.[41] These spontaneous tumors have been transplanted into other rats but they only grew when placed in older animals which were found at autopsy to have tumors in their own hypophyses.[146] This observation indicates that these particular tumors, at least, depend upon an environment attained with advanced age, not only for their origin but for their continued growth.

Lymphoid and Other Tumors in Estrogen-Treated Mice.—Lymphatic leucemia appears frequently in mice of some inbred strains and rarely in animals of other strains.[147] Lymphoid tumors have appeared in a great many estrogen-treated mice at incidences sufficiently higher than in the untreated control mice to merit consideration. The implication is not made that these hormones are of etiologic significance in spontaneous leucemia.

Three mice among 111 given estradiol benzoate or estrone benzoate died with lymphoid tumors.[52g] These tumors were transplantable.[148] Fourteen mice from four different strains developed lymphoid tumors when estrogens were injected.[149a] Most of the tumors involved the mediastinum. Tumors of this type were not found in untreated animals of these same strains.

Lymphoid tumors appeared in 15.4 per cent (22 of 140) of the mice of the C_3H strain which had received variable amounts of estrogen. The tumors involved the mediastinum in nearly all cases and frequently many other tissues were invaded or a generalized leucemic picture attained. A similar tumor occurred in 1 of 203 control mice which had received nonestrogenic material or no treatment.[149b] The greater number of tumors appeared among the groups receiving the larger doses of hormone.

The incidence of lymphoid tumors was also increased among mice of another strain when large amounts of estrone were injected[150] or when pellets of stilbestrol were implanted.[126] Others have not noted an increase in the incidence of lymphoid tumors.[53c]

Why estrogens might increase the incidence of lymphoid tumors under such conditions is unknown. Mice treated with x-rays[151] or carcinogens[152] also have shown an increased incidence or earlier appearance of lymphoid tumors. Estrogens will result in atrophy of thymus[153] and probably other lymphoid tissues. Lymphoid tissues are very susceptible to x-rays. It is possible that the malignant transformation of the lymphoid tissue subsequent to the exposure to the different agents mentioned may have some common basis.

Other Tissues in Which Tumors Have Appeared in Estrogen-Treated Animals.—A number of investigators have observed spindle-celled sarcomas arising at the sites of injection of oily solutions of estrogens.[154] Some sarcomas have appeared in mice receiving nonestrogenic substances as well.[154c] The incidence of such tumors was low and they have not been reported among mice bearing pellets of estrogens. At this time the significance of these observations might be questioned.

Female mice of one strain showed a very high incidence of bone tumors.[155] The incidence was always higher among the females than among the males, about 75 per cent and 26 per cent showing osteogenic tumors at an average age of 16 to 18 months, respectively. The tumors were frequently multiple and ranged from osteomas to osteogenic sarcomas.[156] The administration of estrone increased the incidence of bone tumors in males and decreased the age at which they appeared in both sexes.[157]

The bones of animals of some species are greatly modified when estrogens are injected. The long bones of chickens and rats may be made increasingly opaque to x-rays and their longitudinal growth depressed.[158] In mice the pubes are partially resorbed and the marrow cavities of the long bones become replaced by compact bone.[159] These changes may be prevented if the androgen, testosterone propionate, is given with the estrogen.[160]

Although these experiments indicate that estrogens may directly or indirectly affect the proliferation of osseous tissues, osteogenic tumors have been reported only by Pybus and Miller.[155-157] This would indicate that, as with the mammary, pituitary, and testicular tumors arising in estrogen-treated animals, specific factors or agents in addition to the hormone are essential.

The Adrenal Glands in Relation to Experimental Tumors.—The adrenals are affected, probably indirectly, by the injection of estrogens.[153] These glands have been studied extensively in estrogen-treated mice.[32, 137c, 161] A perimedullary degeneration (brown degeneration) of the cortex occurs in estrogen-treated animals and in untreated mice of some strains.[162] These lesions sometimes involved the medullary areas and were associated with the tendency of the mice of strains bearing them to acquire mammary tumors.[163] Strain differences in the persistence of the X-zone of cancer-resistant and cancer-susceptible strains have been observed.[32, 165]

The adrenal lesions of estrogen-treated male mice were more extensive than those of the females and were correlated with the tendency to have hypophyseal tumors.[53c] Similar adrenal lesions appear in rabbits with mammary or uterine tumors.[43, 44]

Effect of Sex Hormones on Growth of Tumors.—Two other aspects of the endocrine-cancer problem are (1) the influence of hormones on tissues after their growth is no longer restricted and (2) the effects of

growing cancers on the genital tissues or functions. The former point is of considerable practical and theoretical significance and will be discussed. It has been mentioned that some tumors of the testes and hypophyses were transplantable only in estrogen-treated animals such as the animals in which they arose. These tumors might either depend on the hormones for their stimulation or directly or indirectly, for the environment created by the hormone. Greene[42-44] has emphasized the acquisition of malignancy which he can demonstrate so well in his rabbits as a series of progressive stages involving hyperplasia, anaplasia, local invasiveness, and finally malignancy and complete autonomy. It might be safe to assume that some tumors, especially the more obviously benign ones, might not survive or proliferate in all environments, while those more obviously malignant, might be autonomous. There is no evidence that sex hormones will alter the rate of growth of mammary adenocarcinomas in mice. Testosterone was without effect.[90, 91] Hypophysectomy did not prevent or greatly reduce the rate of growth of spontaneous mammary tumors.[166]

The growth of transplanted sarcomas was not appreciably changed by the injection of estrogens.[167] Doses of estrogen large enough to induce dwarfism failed to prevent the growth of benzpyrene-induced tumors.[168] One transplanted mammary adenocarcinoma showed inhibited growth and secretory activity when estrogens were injected.[168b]

The growth of the more benign tumors is altered by changes in the environment in which they grow. A transplanted mammary fibroadenoma was largely fibrous when growing in young or aged rats. The incidence of successful grafts was higher in females than in males and was greatly reduced by ovariectomy.[169] Transplanted fibroadenomas grew rapidly in pregnant rats and the epithelial components increased. The growth of other mammary fibroadenomas was not altered by pregnancy[170] nor were sarcomas.[171] The earlier investigations have been reviewed previously.[170] Transplanted mammary fibroadenomas growing in rats receiving testosterone propionate showed a progressive loss of epithelial elements, and some eventually became fibromas.[172]

The resistance of hosts to transplanted tumors partially "immunized" to the transplanted tumors was increased by the injection of estrogen, but not altered by androgen.[173]

INTERPRETATION

A large amount of detailed information on the appearance of tumors in experimental animals given estrogens has been recorded. Mammary, uterine, hypophyseal, testicular, lymphoid, and osteogenic tumors appear in animals of some species or strains when they are exposed to estrogens for prolonged periods. Among mice the mammary, hypophyseal, testicular, and osteogenic tumors are restricted by factors or influences transmitted by the maternal parent or parents to their young.

These factors (hereditary or genetic) or influences (milk influence[61] or mammary tumor inciter[174]) restrict the carcinogenic response of specific organs to animals of certain groups. The estrogens are required before these responses may occur. Estrogens, directly or indirectly, affect the tissues giving origin to these tumors, but the tumors appear only in susceptible animals.

The uterine cervical tumors in estrogen-treated mice and to a lesser extent the lymphoid tumors have not revealed, as yet, other accompanying transmitted factors or influences essential for the establishment of these malignancies. This does not mean that they do not exist because all possibilities have not been investigated.

One might search for some common change elicited by estrogens in the different tissues or organs to indicate the mechanism whereby the tumors arise. The growth-stimulating action of estrogen is not adequate to explain the lymphoid tumors or even those of the genital tissues since the tumors of these latter tissues do not appear during the active growth phases but rather after the greater part of the tissue has become somewhat refractory. In other words, it may be that estrogens increase the physiologic age of the tissues so that other factors may facilitate the establishment of malignancy. There is little doubt that continuous and excessive estrogenic treatment will result in changes indicative of tissue damage in the organs in which tumors arise.

It will be difficult to advance some aspects of the problem of the action of estrogens in carcinogenesis until more is known of the mechanism whereby they act on normal cells to augment the anabolic and proliferative functions, and what limits the capacity of these cells to respond. The possibility that estrogens may be altered chemically and that the products formed are carcinogens might be mentioned, but the metabolic derivatives of estrogens are still being investigated.

According to the definition given earlier, estrogens are carcinogenic. There is evidence, however, that they merely facilitate the materialization of certain potentialities which are transmitted to the organism. For practical purposes it might be well to consider them as possibly carcinogenic when administered continuously, although the investigators in these fields may find increasing evidence to doubt their direct participation in malignant transformations of body tissues.

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EXPERIMENTAL INVESTIGATIONS CONCERNING THE ROLE OF THE PITUITARY IN TUMORIGENESIS

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THE main object of this review is to survey the experimental medical literature concerning the influence of the hypophysis on tumorigenesis in general and the role of hormones in eliciting tumor formation in the pituitary itself. Accordingly, we shall subdivide our material into two principal sections; the first will be concerned with the effect on tumor formation of deficiency or excess of pituitary hormones, while the second will deal with the formation of pituitary tumors in animals treated with hormones of other glands. A brief additional section will be devoted to the few available data on morphologic changes in the anterior lobe elicited by experimental tumors.

EFFECT OF THE PITUITARY ON TUMOR FORMATION

Since the pituitary is largely responsible for somatic growth in general, it has often been assumed that the "growth hormone," produced by this gland, may play an important part in pathologic growth as well. Yet experiments designed to demonstrate a definite action of the anterior lobe on experimental tumorigenesis have been rather disappointing. This is perhaps not as surprising as it may appear at first sight. The growth of individual organs and tissues is not seriously inhibited by *hypophysectomy*. Thus we found,[107] and several other investigators[33, 34, 78, 116] confirmed, that the regeneration of kidney tissue following partial nephrectomy, as well as the healing of skin wounds, is not prevented by hypophysectomy even though somatic growth ceases. This, we felt, indicates that the hypophysis determines only the proportionate increase in the size of the body as a whole but has comparatively little effect on the growth-promoting action of stimuli affecting individual cell groups. Since tumor cells are notoriously independent of the rest of the soma, it is perhaps understandable that they are not specifically dependent upon hypophyseal control, except secondarily inasmuch as the pituitary hormones influence the tissues of the host organism in which the tumor cell lives.

In view of these considerations it does not appear profitable to devote a great deal of space to a critical discussion of the numerous theories concerning the influence of the hypophyseal hormones on tumorigenesis and we shall limit ourselves to a brief survey of the relevant facts reported in the literature.

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Let us consider first the effect of experimentally induced pituitary deficiency.

In the guinea pig Vargas[111] noted that hypophysectomy does not prevent the production of peritoneal fibromatosis by estradiol.

In the mouse x-ray treatment of the pituitary region retards the growth of spontaneous mammary carcinomata in cancer-susceptible strains, especially if the tumor appears at the period of maximum body weight retardation.[15] In hypophysectomized mice Korteweg and Thomas,[55, 56] found that the growth of transplantable and 3,4-benzpyrene tumors is retarded. On the other hand, Gardner[32] noted that in mice hypophysectomized during pregnancy or lactation, mammary cancers can develop even after ablation of the hypophysis.

In the rabbit Lascassagne and Nyka[62] were unable to influence the growth of transplantable carcinomas by pituitary destruction.

In the rat Bischoff and his associates[13, 15] found that roentgen and radon irradiation of the pituitary region significantly retards the growth of transplantable rat sarcoma "R 10" and "carcinoma 256." In the case of the carcinoma the growth rate of the tumor is restored by anterior lobe extracts. Hypophysectomy also retards the growth of the Walker rat tumor.[4, 72, 98] Irradiation of the pituitary is much less effective in this respect.[97] The retardation of the tumor growth rate is approximately the same, however, if the hosts are inadequately fed, so that their body weight increase is inhibited to the same extent as by hypophysectomy.[77] Tumors, produced by subcutaneous injection of dibenzanthracene, also show a decreased growth rate in the hypophysectomized rat.[3] The growth of the Jensen sarcoma is likewise inhibited by hypophysectomy but restored by subsequent anterior lobe therapy. At the same time the O_2 consumption of the tumor is decreased while the anaerobic glycolysis remains normal.[91-93] The glycogen content of the "Walker 256" tumor is inversely correlated with its growth rate and is increased by hypophysectomy.[5] In the case of rat sarcoma "E-2" and "E-5" the retardation in the growth rate following hypophysectomy is not very evident and Franseen and McTiernan[31] were unable to detect any difference in the metabolism of Walker tumors taken from normal and hypophysectomized rats. Mori[83] believed that he saw some inhibition of tumor growth after hypophysectomy, but gave no details.

It should be mentioned in this connection that hypophysectomy facilitates the production of uterine metaplasia by steroid hormones. While in normal rats this lesion is only produced by estrane derivatives, in hypophysectomized rats, androstane and even pregnane derivatives may cause such metaplasia.[105] The question arises whether this change in susceptibility is due to a derailment in steroid metabolism which would lead to a transformation of the androstane and pregnane molecule into more "tumorigenic" compounds.

The development of deciduomas is inhibited by hypophysectomy, but the growth of placenta tissue may proceed in the absence of the pituitary apparently because it is governed by hormones produced by the placental cells themselves.[101]

In man, Lambadarides[63] claimed to have noted some improvement after irradiation of the pituitary region in patients suffering from various types of cancer.

The effect of *pituitary hormone administration* on tumorigenesis has been reviewed by Möller,[82] Grassmann,[35] Lacassagne,[60] and Mori and Nakamura.[84]

In the fowl Sugiura and Benedict[110] were unable to influence the growth of "sarcoma 1" by various pituitary extracts.

In the guinea pig Hofbauer[46-48] found that "leucoplakia" (interpreted as a precancerous change) develops in the cervix uteri under the influence of various anterior lobe preparations.

In the mouse Gross[36] claimed that the growth of transplantable sarcomas is apparently accelerated by certain pregnancy urine extracts, while human placenta implants retard it. The results of subsequent investigators[44, 99, 100, 114] were rather contradictory and difficult to interpret. Sugiura and Benedict[110] state that the Bashford mouse "carcinoma 63" is not influenced by anterior lobe preparations. Bischoff and co-workers[15] state that growth hormone preparations have no clear-cut effect on mouse "sarcoma 180" and similar negative results have been reported concerning the same tumor by giving posterior lobe extracts.[70] Zondek and associates[122] claimed that a mixture of F.S.H. (follicle stimulating hormone) and L.H. (luteinizing hormone) prepared from urine, exerts a significant inhibiting effect on Ehrlich's mouse carcinoma. This was confirmed by many others.[18, 28, 29, 67, 68] Krehbiel and co-workers[58] were unable, however, to influence the growth of mouse "sarcoma 180" by gonadotropic preparations. According to Lustig and Wachtel,[66] even posterior lobe extracts exert an inhibitory effect on certain transplantable mouse tumors, but this is hardly a specific effect and may merely be due to the toxicity of these preparations.

The spontaneous mammary carcinomas of the mouse are not influenced by doses of gonadotropic pregnancy urine preparations sufficient to cause a pronounced enlargement of the ovaries. These experiments, performed by Bischoff and Long[9] on the Marsh-Buffalo strain, led them to conclude that carcinogenesis induced by exogenous folliculoid hormones or estrogens may be without physiologic significance. It must be kept in mind, however, that under the influence of such treatment the ovary would secrete other hormones as well as folliculoids and these other principles (for example, progesterone) may have an anticarcinogenic action. Later, Bischoff and co-workers[10, 11] found that F.S.H. delays the onset of carcinogenesis, while L.H. has no such effect in this strain, although both preparations stimulate mammary growth.

Transplants of anterior lobe tissue increase mammary tumorigenesis, but only in strains having a fair degree of hereditary susceptibility. They are ineffective after ovariectomy.[64, 65] Cramer and Horning[23] claimed that thyrotropic extracts exert an inhibitory action on the development of "R III" strain breast cancers but this could not be confirmed by Haagensen and his associates[42] and it appears probable that the effect of the thyrotropic hormone is merely due to interference with breeding, and in the nonbreeders of course the carcinoma rate is comparatively low.[19, 20] Lacassagne[61] clearly showed that the mammary carcinogenesis obtainable by folliculoids in the susceptible "R III" strain is not inhibitable by thyrotropic hormone treatment. The entire question is quite unsettled, however, since Bischoff and associates[16] report more recently that they were unable to influence mammary carcinogenesis in Marsh-Buffalo mice receiving chronic treatment with pregnant mare serum or sheep anterior lobe extracts, irrespective of whether the treatment caused pronounced ovarian enlargement or gonadal atrophy due to antihormone formation.

The effect of anterior lobe preparations on uterine carcinogenesis has not been adequately studied in the mouse but Loeb and Kirtz[65] state that precancerous lesions in the cervix have been observed repeatedly after anterior lobe transplantations.

In the case of tar cancers gonadotropic pregnancy urine extracts exert no favorable effect,[52] although Katz[54] claimed to have noted an inhibitory and Zeldenrust[117] a stimulating action. Anterior lobe extracts inhibit the growth of such tumors according to Vassiliadis,[112] but it is highly probable that the observed effects were not due to specific hormone actions.

In the rabbit Seel[100] claimed that posterior lobe extracts delay the development of tar cancers and a similar inhibitory effect of posterior lobe preparations has been described by Narimatsu[85] for Kato's transplantable rabbit sarcomas. On the other hand the transplantable Shope papillomas of the rabbit are not influenced by various anterior lobe preparations.[24] Pierson[88] observed a variety of uterine tumors in rabbits chronically treated with gonadotropic pregnancy urine extract. Most of these were characterized by the formation of adenomatous endometrial polyps. Furthermore, the endometrium grew through the uterine wall so that finally it emerged under the serosa resembling the condition of endometriosis. Although such tumors may appear spontaneously in rabbits,[69, 89, 109, 113] they are extremely rare so that there is little doubt of their having been due to the gonadotropic hormone treatment in the previously mentioned experimental series.

In the rat Bischoff and associates[13, 14] noted a slight increase in the growth rate of "transplantable sarcomas and carcinomas" following treatment with crude anterior lobe extracts, but they gave no details. Wiesner and Haddow[115] stated that Jensen sarcomas are not signifi-

cantly influenced by anterior lobe preparations, while gonadotropic pregnancy urine extracts tend to stimulate their growth. Sugiura and Benedict[110] were unable to influence the growth of the Sugiura rat sarcoma, the Flexner-Jobling sarcoma, or the Jensen sarcoma by anterior lobe preparations. Reiss[91] and co-workers[93] claimed that gonadotropic preparations made from pregnancy urine tend to inhibit the growth of Jensen sarcomas while anterior lobe growth hormone extracts slightly stimulate it. Indeed, Baroni and associates[6] state that the growth of the Jensen sarcoma is stimulated by posterior, as well as by anterior lobe extracts. Magath and Smoilowskaia[68] confirmed the inhibitory action of gonadotropic pregnancy urine extracts on these tumors. Druckrey[25] pointed out, however, that the inhibitory effect is more marked in impure than in highly purified extracts of this type. The growth of sarcomas "E-2" and "E-5" do not appear to be stimulated by growth hormone preparations.[27] The results obtained by Robertson and Burnett[94, 95] concerning the action of anterior lobe extracts on transplantable rat carcinomas gave no clear-cut results. Bischoff and Maxwell[12] concluded that "Pronounced gonad stimulation by pituitary extracts and by activated prolan as measured by 300 per cent increases in ovarian and seminal vesicle weights failed to affect the growth of sarcomas R 10 and 180." Heiman[45] claimed that in female rats, gonadotropic pregnancy urine extracts cause a slight decrease and in males a considerable increase in the incidence of takes following transplantation of mammary fibroadenoma tissue.

In vitro the fibroblasts of rat sarcoma tissue grow equally well in a medium containing pituitary extract as in one to which embryonic extract has been added.[2] Long-continued injections of pituitary or pregnancy urine gonadotropic extracts may result in the formation of adenomatous or fibroadenomatous growths in the rat.[50]

In man no striking effect was obtained by the administration of posterior lobe extracts to carcinomatous patients.[49] On the other hand Hübscher[51] described the case of a woman with an adenocarcinoma of the ovary in whom the growth of the tumor was greatly stimulated by a gonadotropic extract of pregnancy urine.

Summarizing the results discussed in this section it may be said that there is no definite evidence of any direct action of pituitary hormones on tumorigenesis. It is well established however that through its effect on the steroid hormone-producing glands, the hypophysis may exert an important indirect effect upon the growth of tumors and on the condition of the host's tissues.

PRODUCTION OF PITUITARY TUMORS BY HORMONE TREATMENT

The most dramatic effect of hormones on the development of pituitary tumors is that elicited by the folliculoid compounds. In 1936, Cramer and Horning[21, 22] noted that in the mouse a marked enlarge-

ment of the pituitary with the formation of chromophobe adenomas is obtained following continued treatment with folliculoids. Even in those animals in which actual tumors did not occur, the chromophil cells lost their granules so that almost the entire anterior lobe consisted of chromophil cells. The greatly enlarged anterior lobe of these animals showed numerous hemorrhages and generalized hyperemia. Independently, and almost simultaneously, we were able to show[106] that in rats daily administration of 500 gamma of estrone practically doubles hypophyseal weight within twelve days, and that occasionally this treatment may lead to the formation of cavernous anterior lobe adenomas.[77] These observations have repeatedly been confirmed with folliculoid estrone and stilbene derivatives.[26, 86, 87, 119-121] Zondek's attempt to transplant these adenomas proved unsuccessful.[121] Nelson[86] made a particularly detailed and instructive study of these tumors describing the functional changes (visual disturbances, nystagmus, ataxia, etc.) which result from the pressure exerted by these large tumors on the brain. Curiously, the rabbit does not appear to respond in this manner since Zondek[119] and Mazer and co-workers[71] state that even massive doses of folliculoids cause no significant enlargement of the hypophysis in this species. It is perhaps worth mentioning that in rats receiving prolonged treatment with folliculoids, pigmented adenomas of the intermediate lobe have also been observed.[74, 75] In view of the great rarity of intermediate lobe tumors in human pathology, these observations deserve some attention even though the incidence of middle lobe tumors in folliculoid treated animals is extremely low in comparison with the almost constant development of anterior lobe tumors under similar experimental conditions.

The production of anterior lobe tumors with folliculoid hormones is one of the most obvious experimental facts showing the existence of a definite correlation between the hypophysis and tumorigenesis. As stated in the first part of this review neither pituitary deficiency nor overdosage with hypophyseal hormones exerts any very constant and significant effect on tumor growth except perhaps through the intermediary of steroid hormones which are liberated from other endocrine glands under the influence of hypophyseal hormones. In this sense, for instance, the well-known effect of the folliculoids on mammary tumorigenesis in the mouse may be regarded as under pituitary control since the formation of folliculoids by the ovary is regulated by gonadotropic hormones. The production of hypophyseal adenomas on the other hand is apparently a direct effect of the folliculoid compounds and because of the regularity of its appearance serves as an excellent test object for the study of pituitary tumorigenesis in general. It is for this reason that these growths deserve special attention.

It is well known that a large number of steroid hormones possess an "antifolliculoid" effect, that is to say, are capable of inhibiting certain

folliculoid actions. This potency of steroids has been discussed elsewhere in detail[103, 104] so that here it will only be necessary to summarize those aspects of the problem which are pertinent to the subject of pituitary tumorigenesis. It has been found that most, if not all, hormonally active steroids, other than the folliculoid estrane derivatives, are antifolliculoid to some extent. Thus, they can inhibit the vaginal cornification, the involution of the seminiferous epithelium, and the uterine estrus as well as the enlargement of the adrenal cortex and pituitary which are normally elicited by folliculoids. While only this latter effect is of interest in connection with the problem under discussion, it must be emphasized that there is no close parallelism between the various antifolliculoid actions of the individual steroids. A compound may be very active in inhibiting one, but comparatively inert with regard to another folliculoid action. From the practical, clinical point of view it would obviously be of great interest to detect steroids which have a specific antitumorigenic action.

A large number of steroids have been studied in our laboratory for their ability to inhibit tumorous growth using the hypophyseal enlargement and tumorigenesis elicited by α-estradiol, as a test object. It soon became evident that testosterone is very active in this respect.[102] Subsequent investigations confirmed this effect of testosterone and showed that methyl-testosterone is approximately equally active while Δ^5-*androstene*-3(β),17(α)-diol, Δ^5-*androstene*-3(β)-ol-17-one, and progesterone are considerably less active.[1] A very large number of hitherto unpublished experiments with a great variety of steroids revealed that the diproprionate of Δ^5-*androstene*-3 (β),17(α)-diol is somewhat more active than the free compound and that Δ^4-*androstene*-3,17-dione is perhaps one of the most active compounds so far examined. It is of particular interest that Δ^4-*androstene*-3-one-17(β)-ol (''cis-testosterone'')—which is practically inert as an ''androgenic'' or testoid compound and is extremely inert with regard to all other hormone actions—is among the most potent compounds when tested for its ability to inhibit the effect of estradiol on the pituitary. This action is even more pronounced in the case of the acetate and propionate of this steroid.

There is, of course, no definite proof indicating that the naturally occurring anterior lobe tumors are caused by stimuli similar to those which are responsible for the tumorigenic effect of the folliculoids. Indeed, physiologically there are some striking differences in symptomology. Animals which develop anterior lobe tumors as a result of estradiol treatment have an enlarged adrenal cortex, a tendency toward the diabetic type of carbohydrate metabolism disturbance, definite abnormalities in the development and function of their sex organs, and manifestations due to the local pressure which the enlarged hypophysis exerts on the brain tissue.

It is very probable that these tumorous anterior lobes are capable of producing an excess of certain pituitary hormones especially the

adrenotropic, mammotropic, lactogenic and, perhaps, also diabetogenic factors. On the other hand, judged by the inhibition of somatic growth and the atrophy of the thyroid and gonads, they appear to discharge subnormal amounts of growth-promoting thyrotropic and gonadotropic principles. Especially the inhibition of somatic growth is rather different from the manifestations of hyperactive anterior lobe tumors in man. Yet, even in human pathology the functional manifestations differ depending upon the type of tumorous growth, and the resemblance between these experimental tumors and the spontaneous anterior lobe adenomas of man is sufficiently great to make experimental work concerning inhibition of the rat tumors appear to be of some possible clinical applicability. From this point of view the activity of cistestosterone and its esters is of special interest because these compounds appear to exert a pronounced antitumorigenic action uncontaminated by any significant degree of undesirable hormonal side-effects.

MORPHOLOGIC CHANGES IN THE ANTERIOR LOBE ELICITED BY EXPERIMENTAL TUMORS

Before discussing the experimental literature it may be well, for the sake of comparison, to survey briefly the data concerning hypophyseal changes in tumor-bearing patients.

Tumors of various organs may influence the structure of the pituitary gland. Thus in patients suffering from carcinomas, Karlefors[53] noted a decrease in the eosinophiles and an increase in the main cells. Krieger[59] found that the average weight of the gland is relatively high in cases of malignant tumors. Berblinger and Muth[8] noted an increase in main cells in cases of carcinoma or sarcoma, but they did not consider this to be a specific change and looked upon it merely as the effect of toxic products liberated from the tumor tissue. Saenger[96] observed a tumorlike proliferation of the main cells in the hypophysis of a woman with a large ovarian carcinoma. It seems questionable, however, whether this change should be attributed to the tumor as such, because the patient showed other signs of endocrine disturbances. Puccinelli[90] emphasized the occurrence of large quantities of pigment in the posterior lobe of tumor-bearing individuals. Kraus and Traube[57] state that in carcinoma-cachexia the number of basophiles is usually subnormal. Meessen[79] claimed that in carcinomatous patients, there is increased basophilic invasion in the posterior lobe.

Chorion epitheliomas in man occupy a particular position in so far as they produce gonadotropic hormones. Zondek[118] was the first to note that in such cases the pituitary shows pregnancy changes, a fact which has been confirmed by Erdheim[30] and Siegmund.[108]

With regard to experimental tumors the following observations are noteworthy. Berblinger[7] and Berblinger and Muth[8] showed that treatment with various protein extracts may lead to such changes in the rabbit pituitary as have been seen in carcinoma-bearing human indi-

viduals. In the hypophysis of rats inoculated with the Walker rat tumor, McEuen and Selye[73] observed the appearance of large cells with eccentric nuclei and a granular chromophobe cytoplasm. Some of these cells contain vacuoles of unusual size. Guyer and Claus[37, 38] noted similar histologic changes in the hypophysis of rats bearing the Flexner-Jobling carcinoma and regarded them as identical with those produced by castration. However, we[76] were able to produce similar changes by the intraperitoneal implantation of kidney tissue and concluded that "the changes produced by transplantable tumors are not necessarily related to the malignant growth as such but are at least partly due to decomposition of tissue in the necrotic centers of the tumor." Brown and Pearce[17] noted a slight hypertrophy of the hypophysis in rabbits inoculated with tumor tissue. Hammett[43] reported an insignificant increase in the size of the hypophysis in a rat bearing a "myxocavernous" type of hemangioma which occurred spontaneously in the peritoneum. Mendeléeff[80, 81] claimed that normal guinea pig pituitary tissue increases the coagulability of plasma in vitro while the hypophysis of cancer-bearing guinea pigs is not very active in this respect.

In conclusion it may be said that both the spontaneously occurring tumors of man and the experimental growth of animals frequently produce definite morphologic changes in the anterior lobe, but it remains doubtful whether these should be regarded as specific effects of the tumor as such or merely as a result of toxic metabolites elaborated by the abnormal growths.

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THE ENDOCRINE EFFECTS OF PITUITARY TUMORS

A Clinical Review

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THE early attempts[21] to unravel the anatomic complexities of the region overlying the sella turcica led Galen to apply the term plexus retiformis to these structures. Vesalius, in spite of misinterpretation of anatomic structures, was led to the prophetic statement: "Rete mirabile, in quo vitalis spiritus ad animalem preparentur." For over 100 years, the "wonderful net" retained its secrets, until the keen eyes and wits of Willis separated the net into its component parts, on the basis of comparative anatomic studies. Bridging a gap of almost 200 years into the future, Willis stated: "The ramification of the carotids into a reticulated plexus shows . . . that the blood . . . before it is let into the cerebrum takes some part of the superfluous serum of the pituitary gland and instils another part into the various shoots to be led back toward the heart."

The modern conception of internal secretion was supplied by the brilliant studies of Claude Bernard. In the light of present knowledge, it is somewhat paradoxical that the first demonstration of functional activity of the pituitary by Schäfer (1894), was confined to the posterior lobe (1898).

Clinical interest in the pituitary gland was aroused by Marie's[57] disclosure that the condition he termed acromegaly was usually accompanied by an hypophysial tumor. The allied condition of gigantism had been studied not infrequently, but even the discerning mind of John Hunter had failed to note the enlarged pituitary fossa of the Irish giant's skeleton that he so carefully prepared. In fact, the dust of another century accumulated in the enormous sella turcica before Arthur Keith peered in and grasped its significance. Cunningham previously noted the enlarged sella turcica in this skull by palpating through the foramen magnum. Although an instance of pituitary tumor was recorded as early as 1771 by Greding, the pathologic nature of these pituitary enlargements was not clearly appreciated until Benda (1900)[10]

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differentiated them as pituitary adenomas. There was little difficulty in distinguishing the two common types on the basis of the staining characteristics of their cytoplasmic granules. Those tumors composed of cells with large eosin-staining granules were designated acidophilic* adenomas; those with fine, sparse, poorly staining granules were termed chromophobe. Two small adenomas composed of basophile elements were described by Erdheim (1903)[30] without note as to their possible clinical significance. The basis was thus established for clinicopathologic studies, which had already begun to appear.

It was almost inevitable that these early clinicopathologic reports should be in the form of syndrome delineations and that some of these

Fig. 1.—Marie, Case 1, acromegaly.

should be preserved in eponymic fashion. Since many of these syndromes have a direct bearing on the subject matter of this communication, it may be permissible to quote a few in briefest outline.

MARIE, P. (1886,[57] Case 1, Fig. 1).—A woman 37 years of age had symptoms of thirteen years' duration, consisting of fatigue, amenorrhea, striking enlargement of the extremities, and of the head and face.

*The original designation "chromophil" was later supplanted by "eosinophil" and more recently by "acidophilic" (and "basophilic").

BABINSKI, J. (1900,[6] Fig. 2).—A girl 17 years of age had symptoms of headache, failing vision, epileptiform seizures, adiposity, genital hypoplasia, amenorrhea, and papilledema; autopsy disclosed a large tumor of the pituitary. This tumor was described eight years earlier by Bakinski's student, Orianoff (1892).[59]

FRÖHLICH, A. (1901,[34] Fig. 3).—A boy 14 years of age had symptoms of headache, visual impairment, vomiting, and rapid gain in weight; examination revealed unilateral amblyopia, temporal hemianopia, adiposity, feminine physique, genital dystrophy, scanty hair, and dry skin. This patient was operated upon by von Eiselsberg, in 1907, and a cystic tumor partially removed from the sella turcica; histologic diagnosis was carcinoma or, more probably, an adenoma of the hypophysis in the precancerous stage.

Fig. 2.—Babinski, hypopituitarism.

LORAIN, P. (1871).[56]—A syndrome was described consisting of: (1) weakness, gracefulness, and smallness of the body, as an arrested development affecting the mass of the body; (2) persistent youthfulness; (3) feminine characteristics in males, as broad hips, feminine distribution and character of hair, genital hypoplasia, and development of the breasts.

LEVI, E. (1908,[52] Case 1, Fig. 4).—A girl 20½ years old had developmental arrest since the age of 10 years, headaches, vomiting, amenorrhea, progressive visual failure, optic atrophy, and radiographic enlargement of the sella turcica (nearly 2 cm.).

GILFORD, H. (1897,[37] Case 1, Fig. 5).—A boy 17 years old had arrest of body growth (height 3 feet 8½ inches, weight 35.2 pounds) and premature senility; infantilism and senilism were both present. He died at the age of 18 with small cirrhotic kidneys and atheroma of the coronary arteries. The name progeria was given to this condition by Gilford in 1904.[38, 39]

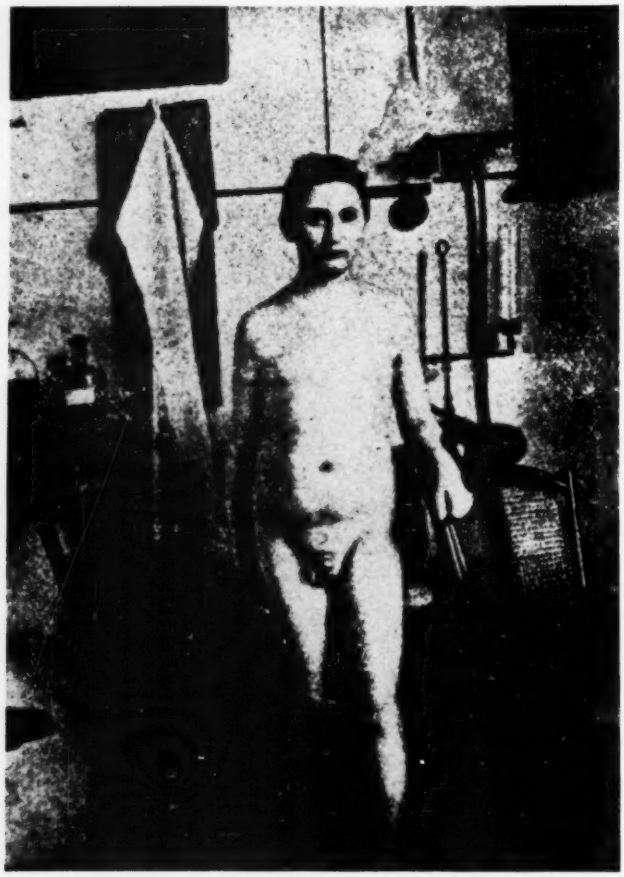

Fig. 3.—Fröhlich, Fröhlich syndrome.

SIMMONDS, M. (1914).[78]—A woman 46 years of age had puerperal sepsis eleven years previously, followed by amenorrhea, asthenia, vertigo, episodes of unconsciousness, emaciation, premature senility, and anemia. Autopsy revealed small abdominal organs, embolic necrosis of pituitary, noninflammatory.

CUNNINGHAM, D. J. (1891).[18]

KEITH, A. (1911,[45] Fig. 6).—The Irish giant, O'Brien (or Byrne), died in 1783 at the age of 22 years. The skeleton, which was obtained by John Hunter and is preserved in the Museum of the Royal College of Surgeons, London, has a stature of 7 feet, 8¾ inches; the sella turcica has an anteroposterior diameter of 21 mm., width 24 mm., depth 11 mm.

THE PITUITARY ADENOMAS

Analyses of the symptoms observed in groups of patients with the various types of pituitary adenomas* afford a logical starting point for the subject under consideration. The analyses will be limited to endo-

Fig. 4.—Levi, hypopituitarism, Lorain-Levi type. Left (Case 2), age 15 yr., 5 mo.; right (Case 1, sister of patient in Case 2), age 20 yr., 6 mo.

crine symptomatology, although this forms only a portion of the total clinical picture. Both positive and negative phases of pituitary functions may be distinguished in these syndromes. Some of the negative

*Craniopharyngiomas are omitted, since their endocrine picture appears to result from combined pituitary and hypothalamic disturbances.

effects may be ascribed to the compression of the normal adenohypophysis by the expanding adenoma. Positive effects are predominant in the acidophilic adenomas while the clinical picture produced by the chromophobe adenomas appears to be one of pure hypopituitarism. The mixed adenomas produce both positive and negative endocrine effects; the situation is still confusing with respect to the basophilic adenomas.

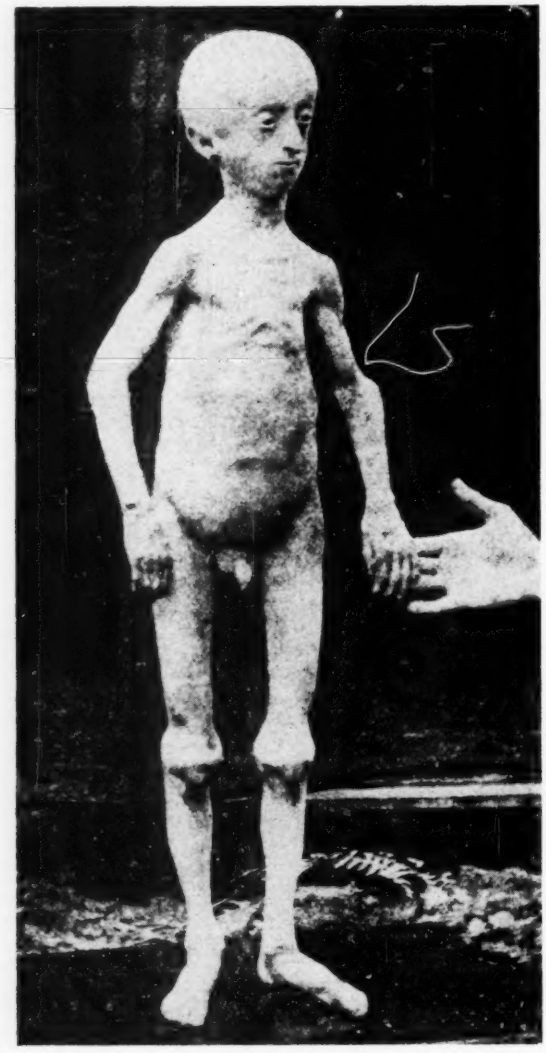

Fig. 5.—Gilford, Case 1, progeria.

Acidophilic Adenomas.—Acidophilic tumors form about 20 per cent of the pituitary adenomas. The clinical picture depends upon the age of the patient at the onset of tumor growth, gigantism being observed in those whose epiphyses have not closed while acromegaly is characteristic of tumor onset during adult life. A mixture of gigantism and acromegaly is not uncommon in young adults. The syndrome produced

by the acidophilic adenomas is likewise dependent upon the phase of tumor growth at the time the patient is observed; cystic degeneration introduces the effects of hypopituitarism into the clinical picture.

The acidophilic cells compose about 37 per cent of the cells of the normal adenohypophysis. Their cytoplasm contains numerous large, acidophilic granules, giving the cytologic appearance of actively secreting cells. The unique observations of Smith and MacDowell,[84, 85] on the congenital absence of acidophilic cells in the pituitary of hereditarily dwarfed mice of the Dunn strain, suggest that the elaboration of the growth factor is dependent upon the acidophilic cells.

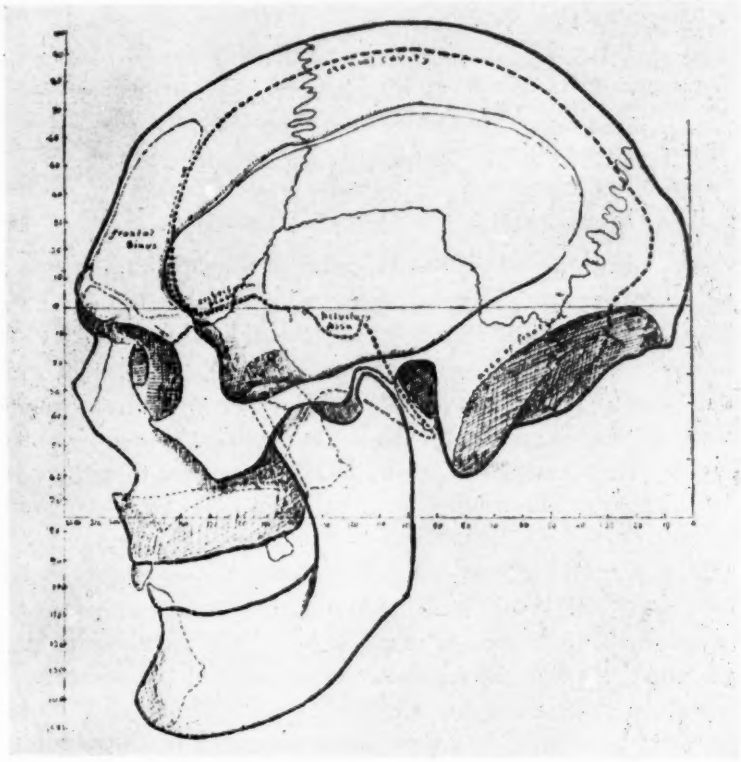

Fig. 6.—Keith, profile construction of O'Brien's skull.

The endocrine effects of the acidophilic adenomas have been tabulated by Davidoff[25] (Table I based upon an analysis of the records of 100 cases from Cushing's series).

More complete evaluation of the significance of these symptoms will be attempted later. It may be noted at this point, however, that most of the endocrine symptomatology is of a positive nature, with tissue overgrowth as a prominent feature. Thus, enlargement of acral parts (100 per cent), hypertrichosis (53 per cent), fibromata mollusca of skin (27 per cent), and possibly increased basal metabolic rate (70 per cent),

TABLE I

ACROMEGALY
(DAVIDOFF, 100 CASES)

SYMPTOM	INCIDENCE (%)
Enlargement of acral parts (Gigantism, 14)	100
Disturbance of menstrual cycle	87*
Complete amenorrhea	73*
Increased basal metabolic rate	70†
Excessive perspiration	60
Hypertrichosis	53
Cutaneous pigmentation	46
Gain in weight	39
Diminished libido sexualis	38
Asthenia	33
Low blood pressure (less than 120 mm. Hg systolic)	30
Polyphagia	28
Fibromata mollusca of skin	27
Polydipsia	25
Enlarged thyroid gland	25
Glycosuria (diabetes mellitus, 12)	25
Decrease of body hair	7
Persistent lactation	4
Failure of breasts to develop	4

*Percentage of female patients.
†Percentage of 70 cases examined.

excessive perspiration (60 per cent), gain in weight (39 per cent), and polyphagia (28 per cent) may be accounted for on the basis of excessive elaboration of the growth factor by the tumor. This tendency toward tissue overgrowth affects the viscera as well, in the form of splanchnomegaly (Cushing and Davidoff[24]). Of other prominent symptoms, disturbance of the menstrual cycle (87 per cent) is undoubtedly a gonadotropic effect and diminished libido (38 per cent) is probably in the same category. The symptoms of asthenia (33 per cent), low blood pressure (30 per cent), cutaneous pigmentation (46 per cent), polydipsia (25 per cent), glycosuria (25 per cent), and enlarged thyroid gland have been referred to as polyglandular effects.

Chromophobe Adenomas.—Chromophobe is the most common tumor of the pituitary, accounting for about 73 per cent of the adenomas. The clinical picture depends upon the age of the patient at the onset of tumor growth, pituitary dwarfism being observed in those patients in whom the tumor is well advanced before adolescence. The endocrine syndrome produced by the chromophobe adenoma is almost the complete antithesis of that due to the acidophile adenoma; it is characterized by hypopituitarism.

The chromophobe cells compose about 52 per cent of the cells of the normal adenohypophysis, according to Rasmussen.[64] These chromophobe mother cells of the normal gland are apparently identical with the cells of the chromophobe adenomas. Although these cells possess no cytologic characteristics of secreting cells, Severinghaus[73] has noted that they contain two distinctive types of Golgi bodies: a net type, characteristic of the acidophile cell, and a ring type, similar to that

of the basophile cell. Thus, the final secretory phase appears to be predetermined in the chromophobe mother cells. Applying this method of study to a few adenomas removed at operation by Cushing,[23] Severinghaus found: "(a) that in the adenoma of acromegaly the Golgi body of all cells, whether chromophobe or acidophilic, is of acidophilic type; (b) that in the chromophobe adenomas the cells with a Golgi body of acidophilic type far outnumber those with a Golgi body of basophilic type." Bailey and Cushing[8] had previously suggested, on the basis of staining characteristics, that "the chromophobe cells are not all of the same nature."

The endocrine effects of chromophobe adenomas are tabulated in Table II, based upon the records of 100 consecutive cases of Cushing's series in the Brain Tumor Registry, Yale University School of Medicine.* The sex distribution was 53 males and 47 females. The age incidence was: second decade, 5; third decade, 14; fourth decade, 23; fifth decade, 33; sixth decade, 19; seventh decade, 5; eighth decade, 1. Since the presence or absence of certain symptoms were not specifically noted on all records, the percentage incidence of symptoms is calculated on the basis of the number of cases in which specific mention of the symptom was found, as well as the total number of cases.

Disturbance of the menstrual cycle occurred in 97 per cent of women between the ages of 15 and 45 inclusive, 94 per cent having amenor-

TABLE II

CHROMOPHOBE ADENOMAS
(100 CASES)

SYMPTOM	INCIDENCE (%)	
	WHERE NOTED	TOTAL
Disturbance of menstrual cycle	78	78*
Subnormal basal metabolic rate (below −5)	77	76
Abnormality of skin (fine, dry)	81	56
Abnormality of hair (distribution, fine, scant)	55	53
Gain in weight	51	47
Diminished libido sexualis	62	39
Subnormal blood pressure	40	39
Diminished potentio sexualis	71	28†
Subnormal temperature	33	23
Somnolence	31	22
Genital abnormality (hypoplasia)	33	15
Polydipsia (slight)	13	12
Mammary hypoplasia		11*
Questionable enlargement of acral parts	12	9
Weakness	10	9
Polyuria (slight)	10	9
Feminine habitus in males		8†
Small acral parts	7	5
Appetence for sweets (slight)	6	5
Small stature	6	3
Glycosuria (slight)	3	2

*Percentage of female patients.
†Percentage of male patients.

*With the kind assistance of Dr. Louise Eisenhardt.

rhea. Of the 15 women over 45 years of age, 40 per cent had amenorrhea before the age of 45. Diminished libido sexualis occurred in 39 per cent of all patients but was noted in 62 per cent* of those whose records contained a specific note concerning it. It was lost in 30 per cent and diminished in 32 per cent. Diminished potentio sexualis was recorded in 28 per cent of all male patients, but in 71 per cent* of those where this symptom was specifically noted. It was lost in 42 per cent and diminished in 29 per cent. In those patients whose genital status was noted, hypoplasia or atrophy was present in 22 per cent and genital infantilism in 11 per cent. Mammary hypoplasia was found in 11 per cent of the female patients while one male exhibited enlargement of the breasts. Feminine habitus appeared in 8 per cent of the males while feminine distribution of the hair was noted in 19 per cent. It is obvious that sexual functions are severely disturbed by the growth of a chromophobe adenoma. Evidence that this disturbance is due to compression of the normal basophilic elements by the expanding adenoma has been presented by Cushing[23] and will be discussed later.

Another group of symptoms is not greatly different from those observed in hypothyroidism. Basal metabolic rates of less than –5 were found in 76 per cent of all cases. Of these, 24 per cent were –6 to –15, and 39 per cent were –16 to –25, while 15 per cent were below –25. There were 20 per cent in the normal range of –5 to +5, and 3 per cent were +5 to +10. The skin was noted to be abnormal (fine, dry) in 56 per cent of all patients. Of these, 46 had fine skin; the skin was unusually dry in 25 and finely wrinkled in 7. Only 2 patients had coarse skin, and excessive perspiration was present in 2. Gain in weight was recorded in 47 per cent of all cases, being only a slight increase in 23 patients but frank obesity was present in 24. Weight loss occurred in 5 cases while 2 patients exhibiting pituitary dwarfism had subnormal weights. Subnormal temperature was found in 23 per cent of all patients and somnolence was noted in 22 cases. It would be tempting to ascribe this group of symptoms to a deficiency in the thyrotropic hormone of the adenohypophysis. However, since the elevated basal metabolism frequently observed in acromegaly responds poorly to thyrodectomy, it appears likely that the pituitary itself is partially responsible. Another bit of evidence in this respect is found in the condition of the hair in patients with chromophobe adenomas. The hair was scant in 47 cases, but this was usually limited to the body hair. Fine hair was noted in 19 patients, while only 2 had coarse hair. Feminine distribution of the hair has already been mentioned in 19 per cent of male patients. This tendency toward feminine type of hair is corroborated by the fact that normal hair was noted in only 13 males as opposed to 28 females. Increased hair was mentioned in one case.

In view of the consistent elevation of blood pressure in cases of basophilic adenoma, it is interesting to note subnormal blood pressure

*The actual incidence probably approximates the higher figures.

in 39 per cent of these patients with chromophobe adenomas. The range of "normal" blood pressure for various age groups has been established by the studies of Robinson[68] and The Life Extension Examiners.[74] In the present series, systolic hypotension occurred in the various age groups as follows: Second decade, 2 of 5 patients had systolic pressures under 100 mm.; third decade, 4 of 13 under 110 mm.; fourth decade, 13 of 22 under 115 mm.; fifth decade, 10 of 32 under 120 mm.; sixth decade, 9 of 19 under 120 mm.; seventh decade, 1 of 5 under 120 mm. Systolic hypertension over 150 mm. occurred in only 4 patients of the 97 whose blood pressure was recorded; systolic and diastolic (over 100 mm.) hypertension was present in 3 patients; all patients with hypertension were in age groups over 40. The average blood pressures for the various ages were as follows: second decade, 109/59; third decade, 111/71; fourth decade, 117/75; fifth decade, 124/80; sixth decade, 128/78; seventh decade, 154/83.

It was a little surprising to find questionable enlargement of acral parts mentioned in 9 per cent of the cases. Undoubtedly the various clinical observers were searching for such changes and it is probably significant that in no case was there unequivocal acral enlargement. However, perhaps this question should not be passed over so lightly since it has already been noted that chromophobe adenomas are composed of cells, the majority of which resemble the normal mother cell of the acidophilic type, on the basis of Golgi body characteristics. It is not impossible, therefore, that some of these cells might mature to the extent of elaborating some internal secretion. Such maturation probably occurs in the mixed adenomas soon to be discussed. The negative phase of acral overgrowth was observed in only 5 per cent of the patients, the same number who sought treatment during the second decade. Small stature was present in 3 per cent. These symptoms are undoubtedly dependent upon the onset of tumor growth before adult proportions have been attained. They are probably related to pressure atrophy of the acidophilic elements of the normal gland by the expanding adenoma within the confines of the sella turcica.

A few other symptoms are worthy of brief note at this time, on the basis of their possible relation to secondary disturbance of other endocrine glands. Possible effects upon the thyroid have already been mentioned. In regard to the pancreas, increased sugar tolerance, although not included in the table of symptoms, is observed, not infrequently, in cases of chromophobe adenoma and will be discussed later. However, symptoms suggestive of pancreatic deficiency were observed as follows: polydipsia 12 per cent, polyuria 9 per cent, increased appetence for sweets 5 per cent, and glycosuria 2 per cent. All these were slight or questionable in degree and it is not unlikely that they were due to pressure upon the hypothalamus. Inquiry was made, in most of the cases, concerning possible adrenal disturbance: subnormal blood pressure in

39 per cent has been mentioned; weakness was a complaint in 10 per cent but abnormal pigmentation of the skin was not observed.

Simmonds's Disease.—Since the endocrine syndrome of chromophobe adenomas is predominantly suggestive of hypopituitarism, the pure state of hypopituitarism as observed in Simmonds's disease is worthy of comparison. This condition is frequently the result of pituitary infarction from severe puerperal hemorrhage or sepsis. Of the 42 cases reviewed by Silver,[77] 10 were due to tumor involving the pituitary as follows: complete destruction of hypophysis by basophilic adenoma, 2;* carcinoma, 2; cyst, 5; "fibroblastic endothelioma of Masson," 1. It is perhaps significant that chromophobe adenoma was not an etiologic agent. The symptoms of Simmonds's disease are shown in Table III, on the basis of the review by Silver.[77]

TABLE III

SIMMONDS'S DISEASE
(SILVER, 42 CASES)

SYMPTOM	INCIDENCE (%)
Cachexia	100
Loss of pubic hair	86
Loss of axillary hair	79
Asthenia	64
Genital atrophy	60†
Amenorrhea	55*
Loss of teeth	36
Progeria	29
Atrophy of jaw	24
Hypothermia	21
Loss of libido	14
Eosinophilia	14
Anemia	14
Hypotension	7

*Percentage of female patients, age 15 to 45 at onset.
†Percentage of male patients.

The most striking disparity between the hypopituitarism of Simmonds's disease and that caused by chromophobe adenomas is the appearance of cachexia in 100 per cent of the cases of Simmonds's disease while gain in weight was noted in 47 per cent of the chromophobe adenoma patients and cachexia was not mentioned in any. Asthenia (64 per cent) in Simmonds's disease is probably related, at least in part, to the cachexia. Abnormality of hair is not dissimilar in the two conditions, but loss of teeth in 36 per cent of the cases of Simmonds's disease is striking in the absence of such change in patients with chromophobe adenomas. Similarly, progeria, noted in 29 per cent of the patients with Simmonds's disease, was absent in the chromophobe adenoma cases. In fact, chromophobe adenomas sometimes seem to have a reverse effect, giving an appearance younger than the actual age (ateleiosis).[46] There is no obvious explanation for the higher incidence

*From the pathologic description of these tumors, it is not unlikely that they were chromophobe adenomas.

of amenorrhea and loss of libido in patients with chromophobe adenoma.

At present there is insufficient ground for more than speculation on the difference in the hypopituitary picture produced by these two conditions. Although certain cases of Simmonds's disease, especially those due to pituitary thrombosis, are characterized by a rapid course, the presence of this syndrome due to tumors causing hypophyseal destruction makes it unlikely that the time factor is of great importance. It appears improbable that the cause of this difference is to be found in the posterior lobe, since the neurohypophysis was reported to be normal in 60 per cent of the cases of Simmonds's disease reviewed by Silver.[77] It is possible that the adenohypophysis is less affected by the pressure of an expanding chromophobe adenoma than it is in Simmonds's disease, even when the latter is due to tumor. However, it is difficult to understand how a significant amount of normal adenohypophysis could be preserved in the presence of a huge, sella-expanding adenoma. Even so, one would expect the difference in the syndrome to be one of degree rather than of kind. It is true that the weight gain, so characteristic of patients with chromophobe adenoma, might be hypothalamic in origin. However, obesity often occurs in the absence of any other signs of hypothalamic disturbance. There remains the possibility that the difference under discussion may be due to the actual elaboration of a hormone by the supposedly functionless cells of the chromophobe adenoma. To date there is no positive evidence for this.

Mixed Ademonas.—In 1910, Cushing[19] stated: ". . . in many of the cases in which existing hypopituitarism is the striking feature traces at least of an early tendency to hyperpituitarism can be detected." Dott and Bailey,[27] on the basis of a study of hypophyseal adenomas from Cushing's Clinic, found 13 examples of mixed adenomas in which "the features of acromegaly and of the hypopituitary syndrome develop synchronously rather than in sequence." In 1928, Bailey and Cushing[8] reported the results of further studies on this acromegalic type of dyspituitarism and applied to it the term fugitive acromegaly. This syndrome was identified in 22 instances of 100 adenomas studied. A method of differential staining was applied to these tissues, using neutral ethyl-violet and orange G, for the identification of alpha granules.[7] The symptoms of fugitive acromegaly are shown in Table IV, based on 22 cases of Bailey and Cushing.[8] Aside from the symptoms noted in this table, the syndrome of the mixed adenomas is similar to that of the chromophobe adenomas.

The symptoms noted in Table IV are usually mild in degree and the clinical picture is generally more suggestive of hypopituitarism than the reverse. In fact, most of the cases in Bailey and Cushing's[8] series were originally classified as chromophobe adenomas. The symptoms of

TABLE IV

MIXED ADENOMAS
(BAILEY AND CUSHING, 22 CASES)

SYMPTOM	INCIDENCE (%)
Coarsening of features	36
Enlargement of hands and feet	27
Excessive height	23
Squaring or tufting of phalanges	23
Normal or slightly elevated basal metabolic rate	18
Hypertrichosis	14
Normal or exaggerated libido	14
Excessive perspiration	9
Persistent lactation	5
Glycosuria	5
Spacing of teeth	5

hyperpituitarism are best described as traces of acromegaly, using the term acromegaly in a broad sense, covering the entire syndrome rather than merely the acral manifestations. The microscopic picture is likewise characterized by relatively scant evidence of acidophilic cellular activity, fine alpha granules usually appearing as a ring in the peripheral cytoplasm. It remains a matter of speculation whether these adenomas represent: differentiation within a chromophobe adenoma, dedifferentiation within an acidophilic adenoma, or a specific mixed adenoma from beginning to end. Bailey and Cushing[8] inclined toward the last hypothesis, suggesting that the alpha cells remain of embryonic type.

Basophilic Ademonas.—Two examples of basophilic adenoma were described by Erdheim,[30] in 1903. In his monograph on *The Pituitary Body and Its Disorders,* published in 1912, Cushing described a case showing a "syndrome of painful obesity, hypertrichosis, and amenorrhea with overdevelopment of secondary sexual characteristics." In the light of present knowledge, this patient probably had a basophilic adenoma of the pituitary.[21] Several similar cases were reported by various authors during the ensuing years but pathologic verification of a basophilic adenoma in a patient with the syndrome of plethoric obesity, amenorrhea, purpuric ecchymoses and cutaneous striae, facial hirsutes, exophthalmos, and vascular hypertension was first reported by Parkes Weber[93] in 1926. However, it was not until several years later (Teel[89]) that the significance of the small basophilic adenoma was appreciated. Our present knowledge of the syndrome of "pituitary basophilism" is chiefly due to the work of Cushing,[22] whose contributions to the subject have been so extensive that the eponym—Cushing's disease—sometimes applied to the condition, is not inappropriate.

The symptoms produced by basophilic adenomas are tabulated in Table V, based upon the review of 47 verified cases from the literature and from Cushing's Clinic, by Eisenhardt and Thompson.[28] The characteristic appearance of these patients includes: round, plethoric face; obesity, sparing the extremities; round shoulders or kyphosis; cutaneous

striae, principally of the lower abdomen; female hirsutism. Since the presence or absence of certain symptoms was not specified in some of the case reports, percentages are calculated on the basis of the number of cases in which specific mention of the symptom was found, as well as the total number of cases.

TABLE V

BASOPHILIC ADENOMAS
(EISENHARDT AND THOMPSON, 47 CASES)

SYMPTOM	INCIDENCE (%)	
	WHERE NOTED	TOTAL
Characteristic appearance	98	96
Amenorrhea	81*	81*
Irregular or scanty menses	16*	16*
Impotentia	92†	92†
Skeletal decalcification	95	85
Blood pressure elevation (above 150 systolic or 100 diastolic)	90	81
Glycosuria or decreased sugar tolerance	70	55
Erythrocytosis	52	36
Exophthalmos	85	23
Elevated basal metabolic rate (above +15)	25	15
Decreased basal metabolic rate (below −15)	25	15

*Percentage of female patients with pelvic organs present.
†Percentage of adult male patients.

The syndrome of pituitary basophilism was found by Crooke[17] in 12 patients whose pituitary glands showed merely a hyaline change in the basophiles. This finding was confirmed by Rasmussen[65] in 3 additional cases. Conversely, Susman[88] reported eight instances of basophilic adenoma without evidence of Cushing's syndrome. Finally, a similar syndrome may occur as the result of hyperadrenalism[12, 47] or thymic tumor.[53] In spite of this apparent conflicting evidence, it appears certain that the syndrome described by Cushing is most frequently related to pathologic changes in the basophiles of the pituitary gland. In fact, Crooke[17] found that the characteristic hyaline change of the cytoplasm of the basophiles of the anterior lobe of the pituitary was present in all clinical examples of the syndrome, whether associated with pituitary, adrenal, or thymic tumor or in the absence of any endocrine adenoma. It is of interest that this hyaline change does not appear in the cells composing a basophile adenoma but is found in the basophiles of the adjacent anterior lobe. The recent article by Thompson and Eisenhardt[90] confirms Crooke's findings (Table VI). The physiologic significance of the Crooke changes is subject to two interpretations: (1) an expression of altered physiologic activity (Crooke); (2) a degenerative change following a period of physiologic overactivity of the basophiles (Severinghaus and Thompson[76]).

In spite of the extensive experimental and clinical work upon the physiology and pharmacology of the pituitary body, critically digested by Van Dyke[92] on two occasions, sufficient definitive data are not yet

TABLE VI

VERIFIED CASES OF CUSHING SYNDROME TO 1940
(THOMPSON AND EISENHARDT)

ASSOCIATION WITH TUMOR	TOTAL NO. OF CASES	PERSONAL EXAMINATION OF PITUITARY	
		NO. OF CASES	NO. OF CASES WITH CROOKE CHANGE
Pituitary adenoma*	60	39	35
Adrenal tumor	22	11	11
Thymic tumor	3	3	3
Arrhenoblastoma	1	1	1
No tumor of any gland	12	9	8
Total	98	63	58

*Of the 60 pituitary adenomas, 49 were reported as basophilic.

available to allow interpretation of the component parts of the syndrome of pituitary basophilism. Identification of the basophiles with a gonadotropic function of the anterior pituitary was suggested by Addison's[1] observation of vacuolization of basophiles following castration in the rat.* Confirmation was added by Engle's[29] discovery of increased gonadotrophic potency of pituitary glands obtained from castrated rats. Smith's[80] demonstration of greater sex-maturing potency in the basophile-rich central core of the bovine anterior lobe, compared with that of the acidophile-rich rind, supplied further evidence. However, the direct application of these experimental data to the syndrome of basophilism is confusing in view of apparent diminution of sex functions in clinical cases.† The appearance of a similar syndrome in certain patients with adrenal tumor suggests that parts of the clinical picture may be mediated through the adrenal glands. In fact, hypertrophy of the adrenal cortex, especially the zona fasciicularis, has been a striking feature in most instances of basophilism. Other portions of this confusing clinical syndrome will be discussed later.

POST-MORTEM FINDINGS

Acidophilic Adenomas.—Additional data concerning the endocrine effects of pituitary tumors have been obtained from post-mortem studies. In spite of numerous individual case reports, there are surprisingly few studies based upon a significant number of cases. A striking exception is found in the monograph on acromegaly by Atkinson,[5] containing analysis of 265 post-mortem examinations. Unfortunately, the source material was apparently not suitable for statistical purposes, although data such as the following occasionally appear: The thyroid in 141 cases of acromegaly was hypertrophied in 57 per cent, cystic in 19 per cent, normal in 16.3 per cent, and atrophied in 7 per cent; the

*Basophilic castration cells do not appear in the guinea pig (Severinghaus).[74] In man, the situation is confusing (Kon[40] and Rössle[60]), in fact some reports (Philipp[63]) suggest that the castration effects may appear in the acidophiles.

†Precocious adolescence, at 10 years of age, was present in Cushing's[28] case (A. D.), but this was followed by amenorrhea three years later.

thymus in 98 cases was persistent in 54.6 per cent. Other endocrine organs are mentioned as follows: The pancreas has been described as indurated, enlarged, normal, or showing islet atrophy; the adrenals have been described as normal, atrophied, enlarged, or containing cortical adenomas; the parathyroids are occasionally enlarged; the ovaries have been described as cystic, fibrotic, sclerosed, or degenerated.

In order to obtain more informative data on the post-mortem findings in acromegaly, from the endocrine aspect Table VII was compiled from the studies of Cushing and Davidoff[24] and of Goldberg and Lisser.[40]

These post-mortem findings serve to emphasize certain specific effects of acidophilic adenoma of the pituitary upon the other endocrine organs. The diverse endocrine changes appear to indicate that these effects are not merely an expression of general organomegaly, although enlargement of organs is as much a characteristic of the disease as is skeletal overgrowth. Examples of the enormous size which may be attained by organs of acromegalics are a liver of 6200 Gm. (Goldberg and Lisser[40]) and a heart weighing 1275 Gm. (Osborne[60]). The importance of cardiomegaly was emphasized by Courville and Mason,[16] who reported evidence of marked heart failure in 75 per cent of 24 patients with acromegaly, 6 of whom died of heart failure with cardiomegaly.

Thyroid.—Of all the endocrine organs aside from the pituitary itself, more data are available on the thyroid gland in acromegaly. The analysis of Atkinson[5] has already been mentioned. The trend toward colloid or adenomatous enlargement of the thyroid, shown in Table VII, is confirmed by the studies of Davis[26] on the thyroid gland in 166 cases of acromegaly. The thyroid was enlarged in 52 per cent, with basal metabolic rate greater than +10. Thyroidectomy was done in 27 cases (5 deaths), 26 of the glands being adenomatous and 23 colloid in type; only 3 glands were hyperplastic. The reduction in basal metabolic rate after thyroidectomy was less constant and less in degree than in hyperthyroidism without acromegaly. Concerning the thyroid enlargement in acromegaly, Cushing and Davidoff[24] stated: "... out of 45 cases which we have tabulated, the gland was below normal weight only in ... 2 cases ...; whereas it was said to have been 'large' or 'very large' in 11 cases; and in the other 29 in which the weights were given the average was 129 Gm. The largest recorded thyroid was in Geddes' case (1909)[36] of 312 Gm. ..."

Parathyroids.—There are very few reports on the state of the parathyroids in acromegaly. These glands were mentioned in 3 of the 8 cases summarized in Table VII, being normal, large, and adenomatous, respectively. The "normal" gland was reported as showing a suggestion of proliferative activity. Slight enlargement of the parathyroids was described by Reinhardt and Creutzfeldt,[66] and Bartlett.[9] A parathyroid adenoma was recorded by Josefson.[44] On the basis of present information it is possible only to state that the parathyroids *may* be

TABLE VII

POST-MORTEM FINDINGS IN ACROMEGALY

CASE	SEX	AGE	DIABETES	SPLANCHNOMEGALY	THYROID LARGE	PARATHYROIDS	THYMUS LARGE	ADRENALS LARGE	PANCREAS	GONAD ATROPHY	CAUSE OF DEATH
Cushing and Davidoff											
1	M	52	–	+	+ Colloid, adenomas	Slight hyperplasia	+	+ Cortical adenomas	Large, few islets	–	Cardiovascular
2	M	40	–	+	+ Colloid		–	+	Normal islets	+ Few Leydig cells	Operative fatality
3	M	35	±	–	+ Colloid adenoma	Adenomas	+	+ Cortical adenomas	Large, large islets	+ No Leydig cells	Cardiac failure
4	F	52	+	+	– Colloid cysts		–	+ Cortical adenomas	Normal	+	Diabetic coma
Goldberg and Lisser											
1	M	37	+		–		+	+ Cortical adenoma, hyperplastic medulla			Anesthesia—N_2O-O_2
2	M	45	–	+	+ Colloid	Large	+	+ Cortical adenomas and hyperplasia		–	Purulent sphenoiditis
3	F	58	+		+ Nodular			– Normal	Few islets	+	Hemorrhage from pituitary adenoma
4	F	43	+					Medullary degeneration		+	Suicide

enlarged or adenomatous in acromegaly. It is hoped that future postmortem reports will include the condition of these glands.

Thymus.—Enlargement of the thymus is a frequent finding in acromegaly; the reported persistence of the thymus in 54.6 per cent of 98 cases by Atkinson[5] has already been mentioned. The thymic enlargement was so striking in the case of Fritsche and Klebs,[33] reported in 1884, that the thymus was thought to be the causative agent. Even Marie[58] was impressed by the thymic enlargement in acromegaly. The thymus was large in 4 of the 6 cases in Table VII in which its condition was recorded; the weight of the organ was 78 Gm. in Cushing and Davidoff's Case 3. The significance of the thymic enlargement in acromegaly is not clear, since similar enlargement may occur in the reverse state of hypopituitarism.

Adrenals.—Enlargement of the adrenals was noted in 6 of the 7 cases in Table VII in which their size was recorded. The greatest combined weight was 43 Gm. in Cushing and Davidoff's Case 2. Adrenals of combined weight of 57 Gm. were reported in an acromegalic by Schultze and Fischer.[72] Cortical adenomas were present in 6 of the 8 cases (Table VII). It is apparent that adrenal hypertrophy, often with cortical adenomas, is characteristic of acromegaly.

Pancreas.—Pancreatic enlargement was noted in 2 of 5 cases shown in Table VII, coinciding with Cushing and Davidoff's[24] calculation of an average weight of 143 Gm. in 14 case reports, analyzed by them. The heaviest pancreas weighed 250 Gm. (Launois and Roy[51]). It is not unlikely that pancreatic enlargement is merely one manifestation of acromegaly. The islands of Langerhans have been described as hypertrophic in some cases of acromegaly. This was true in 1 of 5 cases (Table VII); in the remaining cases the islets were normal in 2 and scanty in 2.

Clinical diabetes was present in 4 of the 8 cases and transient in a fifth case; 1 patient died in diabetic coma. The incidence of diabetes mellitus in 153 cases of acromegaly was found to be 17 per cent by Coggeshall and Root[13]; glycosuria was present in 36 per cent. These observers reported that diabetes was the direct or indirect cause of death in 7 of the 17 known dead among their 26 diabetic acromegalics.

Gonads.—Atrophy of the gonads was noted in 5 of 7 cases in Table VII. The microscopic findings in the testes were as follows: Case 1, normal spermatogenesis and great excess of the interstitial cells of Leydig; Case 2, atrophy with no formed spermatozoa and only a few scattered cells of Leydig; Case 3, advanced atrophy of the tubules with no differentiation of the cells, hyalinization of the interstitial tissue with no cells of Leydig; Case 6, mitotic figures present in the cells of the seminiferous tubules and normal cells of Leydig.

The findings in the ovaries were as follows: Case 4, ovaries small and fibrous; Case 7, ovarian tissue replaced by corpora albicantes and

fibrous tissue, germinal follicles absent; Case 8, dense stroma without evidence of germinal epithelium or follicle development, two small cysts lined with epithelium. Cushing and Davidoff[24] described the ovarian findings in a case previously reported by Cushing.[20] In this instance the ovary might have been "regarded as normal were it not for the history of 3 years of amenorrhoea." There were 4 large, fully developed Graafian follicles, the ova of which appeared normal and ready for ovulation. There were no corpora atretica and only one or two faint relics of old corpora albicantia. It appears that both testes and ovaries may be affected in various degrees in acromegaly, the microscopic picture of these organs varying from normal to advanced atrophy.

Chromophobe Adenomas.—Although chromophobe adenomas are much more common than the acidophilic type, very few post-mortem reports are available in the literature. Cushing and Davidoff[24] stated that they had "only two autopsies to draw upon for desired information." These were apparently Cases 5 and 15 in Cushing's[20] monograph on the pituitary body (1912). The findings in these cases will be mentioned later. In order to obtain a more comprehensive view of the endocrine post-mortem findings in cases of chromophobe adenoma, Table VIII was compiled from the autopsy protocols of 9 cases of Cushing's series in the Brain Tumor Registry, Yale University School of Medicine.*

Thyroid.—The thyroid gland was small or atrophied in 4 of 8 cases, in 2 of which fibrosis was noted. It was likewise small in Cushing's Case 5, but there was excess of colloid in distended acini. The gland was normal in 3 instances, in 2 of which the colloid was mentioned as being abundant. Enlargement of the thyroid was observed in 1 case, the acini being distended with colloid. The trend is obviously toward inactivity of the thyroid gland although an abundance of colloid is not unusual.

Parathyroids.—Specific reference to the parathyroids was found in only two protocols. They were normal in 1 case and fat cell replacement was noted in the other. Further information concerning the parathyroids is certainly desirable.

Thymus.—The thymus was unusually large in 1 case, its weight being 40 Gm. It measured 5 x 3 cm. in a second case. From the absence of specific mention of the thymus in the other protocols, it may be assumed to have been small or absent. In Cushing's Case 5 it weighed 30 Gm. and showed extreme hyperplasia; in his Case 15 it was represented by mere shreds of involuted thymic tissue, containing an occasional Hassall corpuscle. It must be admitted that thymic persistence or even enlargement may be observed occasionally in conjunction with chromophobe adenoma of the pituitary.

Adrenals.—The adrenals were small or atrophic in 5 of 8 cases and normal in 3. In one instance the atrophy was noted to be chiefly in the

*With the kind assistance of Dr. Louise Eisenhardt.

TABLE VIII

POST-MORTEM FINDINGS IN CHROMOPHOBE ADENOMA

CASE	SEX	AGE	THYROID	PARA-THY-ROIDS	THY-MUS	AD-RENALS	PAN-CREAS	GONADS	CAUSE OF DEATH
C. W.	M	62	Atrophy, fibrosis			Normal	Normal	Atrophy, fibrosis	Extradural hemorrhage
C. K.	F	58	Small			Small	Normal	Atrophy	Cardiac failure
W. C.	M	22	Large, colloid		5 × 3 cm.	Small 5 and 6 Gm.	Normal	Atrophy, 14 Gm. each	Postopera-tive
P. H.	M	35					Fibrosis		Sphenoiditis (no opera-tion)
F. K.	M	37	Atrophy, 23 Gm.	Fat re-place-ment	Large, 40 Gm.	Cortical atrophy, 3.4 and 3.2 Gm.	Normal	Atrophy, 11.5 and 12.5 Gm.	Postopera-tive, intra-cranial ex-tension
T. H.	M	49	Normal			Cortical fibrosis	Normal		Cerebral hemorrhage (operation 5 years earlier)
J. A.	M	54	Small			Atrophy	Normal	One normal	Extension of growth
B. K.	M	56	Normal	Normal		Normal	Normal	Atrophy	Postopera-tive (else-where)
M. J.	F	40	Normal			Normal	Some large islets	Atrophy	Septicemia (operation earlier ad-mission)

fascicular zone of the cortex; another showed slight cortical fibrosis, while a third was described as having atrophy of both the cortex and medulla. One pair of "small" glands (5 and 6 Gm.) revealed normal structure microscopically but the cells contained "considerable lipoid." The adrenals in Cushing's Case 5 were described as "very large," with "extreme fatty degeneration of the reticular cells"; the medulla was "exceedingly small" but the cells appeared normal. In his Case 15 the adrenals were "practically normal." The slight but definite tendency toward adrenal atrophy in the presence of chromophobe adenoma of the pituitary is in striking contrast to the reverse tendency in acidophilic and basophilic adenomas.

Pancreas.—The pancreas was reported to be normal in 7 of 9 cases. In one of the remaining cases, slight diffuse fibrosis including the islands of Langerhans was described; in the other, some of the islands were "enormous." In contrast to this last case, Cushing's Case 5 was described as "islets inconspicuous, small, apparently normal." It appears that the pancreas may be expected to be normal in the presence of a chromophobe adenoma of the pituitary.

Gonads.—Atrophy of the gonads was noted in 6 of 7 cases. In the remaining case, one testicle was undescended, small, firm and atrophic;

the other was normal. The histologic picture of the testes was as follows: C. W., moderate atrophy and fibrosis with almost complete absence of spermatogenesis; W. C., "not much spermatogenesis"; F. K., atrophy with loss of germinative epithelium, interstitial cells not identified; B. K., inactive spermatogenesis. In Cushing's Case 5 there was absence of interstitial cells, normal tubules, Sertoli cells present, and some spermatozoa. In his Case 15 there were "normal tubules and spermatozoa but no interstitial cells which can be identified as such."

The ovaries were atrophied in both women in the series. C. K. had a menopause at the age of 52 and was operated upon for a chromophobe adenoma of the pituitary at the age of 53 years. She died of cardiac failure in her fifty-eighth year and the ovaries were "small and atrophic." M. J. had onset of amenorrhea at the age of 30 years and a transphenoidal removal of a pituitary adenoma was done at the age of 40 years. She died from septicemia, the result of urinary infection, six weeks later. The right ovary was replaced by a large cyst; the left ovary was grossly atrophic but its histologic characteristics were not included in the protocol. Unfortunately neither case is suitable for an analysis of the ovarian changes associated with chromophobe adenoma of the pituitary. In the male, gonadal atrophy is a striking feature; it is probable that this is likewise true in the female.

Basophilic Adenomas.—In spite of the fact that the basophilic adenoma has been recognized as a clinical entity only since 1932 (Cushing[22]), a considerable body of information has been accumulated concerning the post-mortem findings. This is due chiefly to Eisenhardt and Thompson,[28] and to the stimulating influence of Cushing. Table IX is compiled from the tabulation of Eisenhardt and Thompson,[28] based upon the post-mortem findings in 67 cases of pituitary basophilism, 47 of the patients having basophilic adenomas of the pituitary. Those patients having merely microscopic conglomerations of basophilic elements, sometimes described as adenomas, were excluded from consideration by Eisenhardt and Thompson.

Pituitary.—Basophilic adenomas rarely attain sufficient size to expand the sella turcica or extend above the diaphragm sellae. Compression of the remaining portion of the pituitary gland is not a striking feature. The most frequent effects noted in the gland itself are the Crooke[17] changes. This hyalinization of the cytoplasm of the basophilic cells of the anterior lobe was definite or questionable in 95 per cent of the 44 cases in which the protocols included it. Its significance was interpreted by Crooke[17] as an expression of altered physiologic activity of the basophilic cells. Severinghaus and Thompson[76] were of the opinion that the Crooke changes represent degenerative manifestations following a period of physiologic overactivity of the basophiles as a reciprocal consequence of inactivation of certain subsidiary ductless glands.

TABLE IX

POST-MORTEM FINDINGS IN BASOPHILIC ADENOMA
(EISENHARDT AND THOMPSON, 47 CASES)

	PER CENT
Pituitary: Crooke changes	
Definite	70
Questionable	25
Adrenal hyperplasia (adenoma 17%)	83
Gonads atrophic	85
Parathyroids:	
Normal	54
Atrophy	23
Hyperplasia or adenoma	23
Thymus atrophic or absent	90
Thyroid:	
Inactive or small	47
Colloid goiter or large	32
Normal	15
Adenomas	6

Adrenals.—Hyperplasia of the adrenals was noted in 83 per cent of the 35 cases in which this feature was included in the protocols. An example of the extreme degree of adrenal enlargement which may occur is the case of Page, Roberts, and Biggart,[61] with adrenal weights of 26 Gm. for the right gland and 34 Gm. for the left. Furthermore, adrenal adenomas were present in 17 per cent of the 35 cases. Although the type of adenoma was not specified in most of the cases, they were presumably cortical in origin. There can be no doubt that adrenal hyperplasia is a prominent feature of the endocrine complex associated with basophilic adenoma of the pituitary.

Gonads.—Gonadal atrophy was reported in 85 per cent of 33 cases in which the protocols contained a definite statement concerning this feature. There was a slight sex difference, atrophy being noted in 8 of 11 males compared with 19 of 22 females. Atrophy of the gonads is unquestionably an outstanding element in the pathologic picture of the basophilic adenomas.

Parathyroids.—Specific reference to the parathyroids appeared in 22 instances, the glands being described as normal in 54 per cent. Atrophy was noted in 23 per cent while hyperplasia or adenoma formation occurred in 23 per cent. The presence of parathyroid adenomas in 4 of the 22 cases is likely significant in view of the skeletal decalcification which appeared in 85 per cent of the entire series of 47 cases (Table V).

Thymus.—The state of the thymus was noted in 20 cases and was reported as atrophic or absent in 90 per cent of this number. It was "large" in 1 patient, a male of 19 years of age, and "persistent" in another, a female aged 20 years.

Thyroid.—The thyroid was described in 34 cases and was reported to be inactive (13 cases) or small (3 cases) in 47 per cent. The thyroid was large (4 cases) or a colloid goiter (8 cases) was present in 32 per

cent. The gland was probably normal (5 cases) in 15 per cent, although "abundant colloid" was mentioned in 1 of these. Adenomas (2 cases) were found in 6 per cent. The variability of the post-mortem appearance of the thyroid gland is not surprising in view of the diverse findings concerning basal metabolic rate: Above +15, 25 per cent; below −15, 25 per cent (Table V).

CLINICAL, PATHOLOGIC AND EXPERIMENTAL CORRELATION

Critical surveys of the field of pituitary endocrinology have been published by Van Dyke[92] in 1936 and 1939. The Association for Research in Nervous and Mental Disease[75] published a monograph on the pituitary gland in 1938. More recent developments in this field have been covered in the yearly volumes of the Annual Review of Physiology by Evans,[31] Thomson and Collip,[91] Soskin,[87] Riddle,[67] Long,[55] Hisaw and Astwood,[42] Houssay and Deulofeu,[43] Pfeiffer,[62] and in brief reviews by Collip[14] and Young.[94] The literature for 1940 to 1942 has been reviewed by Hildebrand and Rynearson.[41] In spite of an amazing amount of experimental studies upon the endocrine functions of the hypophysis,* sufficient data are not yet available for complete explanation of all clinical and pathologic findings previously discussed. Apparently contradictory results in some instances are due to species differences in experimental animals. Another source of conflict is the diverse methods of preparing pituitary extracts. On the basis of the physiologic actions of such extracts, at least sixteen effects might be ascribed to the anterior hypophysis as follows: (1) stimulation of general body growth; (2) thyrotropic effect; (3) probably two gonadotropic actions; (4) adrenocortical effect; (5) adrenomedullary effect; (6) mammary secretory action; (7) diabetogenic, (8) ketogenic, (9) glycotropic and glycostatic actions; (10) liver fat and (11) blood lipoid effects; (12) inhibition of insulin hypoglycemia; (13) inhibition of adrenalin hyperglycemia; (14) lowering of respiratory quotient; (15) specific metabolic principle; (16) chromatophore- and erythrophore-expanding effects. In spite of this imposing list of physiologic effects, it is likely that not more than three, and probably only two cell types, acidophilic and basophilic are responsible for the elaboration of anterior pituitary hormones.

Several factors merit consideration in evaluation of the results of experimental studies on the effects of anterior pituitary extracts. None of the anterior pituitary hormones have been synthesized and few have been isolated in a form approaching chemical purity. Many of the extracts, although having physiologic effects, have not yet been proved to be true hormones. The response of the endocrine system in general, to these biologic products, undoubtedly influences the resultant physiologic picture. In fact, the subsidiary endocrine responses may in turn

*The neurohypophysis is omitted from this discussion since tumors do not arise in the posterior pituitary.

alter the function of the hypophysis. It is not surprising, therefore, that numerous physiologic functions have been attributed to the anterior pituitary. However, the opinion of such authorities as Collip[14] and Severinghaus[75] suggests that the number of true anterior lobe hormones must be very small. The various physiologic effects may be represented by different groupings in two or three protein substances, the true anterior lobe hormones.

The pituitary is now well recognized as the master gland of the endocrine system, a role forecast by Cushing many years ago. The accumulation of a large body of clinical, pathologic, anatomic, physiologic and biochemical studies upon this gland allows, at this time, a considerable degree of correlation in terms of specific cellular function within the hypophysis. There is sound anatomic evidence (Severinghaus[75]) for the belief that a secretory cycle normally occurs in the cells of the anterior pituitary, the chromophobes becoming acidophiles or basophiles by a process of granulation; later returning to the chromophobe state through degranulation. The proportions and appearances of the actively secreting acidophiles and basophiles are strikingly influenced by such changes as pregnancy, castration, hyperthyroidism, or thyroidectomy. Cytologic studies indicate that the chromophobes cannot be regarded as actively secreting cells. At present, indirect experimental evidence must be relied upon to corroborate the clinical and pathologic findings in regard to the specific physiologic secretions of the acidophiles and basophiles respectively. The effects of injections of extracts prepared from human acidophilic and basophilic adenomas might be expected to yield valuable information in this respect; a start in this direction has already been made by Kraus.[50] The anterior pituitary of the dwarf mouse, completely lacking acidophiles (Smith and MacDowell[85]), likewise might be suggested for similar experimental use.

Growth.—Clinical and pathologic evidence—gigantism, acromegaly, organomegaly—presents strong support for the belief that a growth hormone is produced by the acidophiles. The experimental evidence begins with the studies of Smith,[79] in 1918, demonstrating that the growth rate of tadpoles was accelerated by anterior pituitary feeding. In 1921, Evans and Long[32] showed that mammalian gigantism could be produced in the rat by long-continued injection of a simple extract of the anterior pituitary. Two years later Smith and Smith[86] found that growth-promoting effects could be produced by ox pituitary tissue composed of acidophiles and chromophobes but not by tissue composed of basophiles and chromophobes. The absence of acidophiles in the pituitary of dwarf mice (Smith and MacDowell[84]) has already been mentioned.

More recent developments indicate that the growth factor may be separated from other fractions of pituitary extracts. The chief function of the growth hormone appears to be the general control of orderly

body growth. Epiphyseal closure follows hypophysectomy and this may be prevented in experimental animals by injections of the growth factor. The growth effect of anterior pituitary extracts is absent in thyroidectomized rats and is increased by the combination of growth and thyrotropic factors. Human gigantism may be arrested and epiphyseal closure effected by administration of testosterone. Growth is depressed by estrone or estradiol therapy; however, immense doses of estrogen are followed by acidophilic hyperplasia of the human anterior pituitary. Growth ceases in intense diabetes in spite of injections of anterior pituitary extract containing the growth factor.

Gonads.—Clinical and pathologic studies leave little doubt that gonadal function is altered—amenorrhea, impotentia, loss of libido—in the presence of either acidophilic or basophilic adenomas of the pituitary. However, the exct nature of this alteration is not clear at present. The microscopic picture of the gonads in acromegaly varies from normal to advanced atrophy; the atrophy, in the testes, apparently involves both tubules and interstitial cells. The cytologic changes in the gonads in pituitary basophilism is likewise uncertain. Of 16 cases reviewed by Cushing[21] the ovaries were "senile" in Case 3; there was "follicular atresia" in Case 4; they were "small but histologically normal" in Case 6; in Case 7 "the ovaries were enlarged apparently from increase in stroma; there was a single large corpus luteum with a small central hemorrhagic area and several smaller ones in various stages of organization." The testes in Case 9 showed "fibrosis with atrophic changes, though some active spermatogenesis was still present"; in Case 10 spermatides, spermatoblasts, and spermatozoa were absent and the interstitial cells were diminished.

Cytologic studies of the pituitary following castration in the rat reveal a marked increase in the number of basophiles, with vacuolated cytoplasm, and a decrease in size and number of acidophiles. Similar changes in the basophiles of the castrate human hypophysis were found by Biggart,[11] but varying response of the acidophiles was noted. The cellular changes in the hypophysis of the guinea pig during pregnancy have been shown by Kirkman[48] to consist of an increase of degranulated basophiles rich in mitochondria—evidence of active secretion; prior to parturition a significant increase of acidophiles occurs. Similar changes have been noted in the human hypophysis by Severinghaus.[75] The correlation of these changes with the physiologic evidence of large quantities of gonadotropic hormone appearing during pregnancy is complicated by the fact that a luteinizing factor (prolan) is produced by the chorionic epithelium of the placenta. However, it appears that the anterior pituitary produces a luteinizing factor, at least during the early phase of pregnancy; there is reason to believe that this factor is elaborated by the basophiles. The hypophysis of the human fetus, lacking basophiles, appears to contain small amounts of follicle-stimulating hormone but no luteinizing hormone (Philipp[63]).

Recent experimental developments, based upon the pioneer work of Smith and Engle[83] and Zondek and Aschheim,[95] indicate that two separable fractions of gonadotropic hormone are probably produced by the anterior pituitary: (1) follicle-stimulating hormone (F.S.H.), necessary for follicle maturation; (2) luteinizing hormone (L.H.). A third factor (leutotropin) has been suggested, necessary for the secretion of progesterone by the corpus luteum, and possibly related to the lactogenic factor of the anterior pituitary. Tubular growth in the testes is dependent upon the follicle-stimulating factor; the luteinizing factor or interstitial cell-stimulating hormone (I.C.S.H.) is responsible for maintenance of the interstitial cells of the testes and production of male hormone. The production of estrogen by growing ovarian follicles is dependent upon the combination of F.S.H. with a small amount of L.H. Ovulation and corpus luteum formation require a level of L.H. much higher than that necessary to maintain the interstitial cells of the ovary or testis. Numerous studies have been made upon the effects of estrogen therapy upon the pituitary. There are cytologic evidences for increased secretory activity by both acidophiles and basophiles, especially the latter; excessive doses of estrogen may result in extreme enlargement of the pituitary and "adenoma" formation. The decrease in F.S.H. and L.H. potency of the pituitary (animals and human) following estrogen therapy may be explained by release of gonadotropic hormone from the pituitary (Severinghaus[75]). Testosterone apparently decreases the gonadotropic potency, especially L.H. of the rat pituitary.

Thyroid.—The frequent occurrence of thyroid enlargement, usually of the colloid type, and increased basal metabolic rate in acromegaly suggest that a thyrotropic factor may be secreted by the acidophiles. The effects of pituitary basophilism upon the thyroid are less constant, although the thyroid is enlarged in about one-third of the cases and the basal metabolism elevated in about one-fourth.

Cytologic studies of the anterior pituitary after thyroidectomy indicate that both types of chromophiles are affected; there are loss of acidophiles and castration-like changes in the basophiles. Experimental hyperthyroidism results in evidences of increased secretory activity of the acidophiles, but the basophiles demonstrate castration-like changes with increase in size and number and vacuolization.

Experimental evidence for the dependence of thyroid activity upon the anterior pituitary, previously suspected, was placed upon a sound basis by Smith.[81] The thyroid atrophies after hypophysectomy and the basal metabolic rate is decreased. Hyperplasia of the thyroid and increased basal metabolic rate follow injections of appropriate anterior pituitary extracts. The thyrotropic factor appears to be a separable fraction of the anterior pituitary, affecting the thyroid by: (1) influence on the rate of discharge of secretion and (2) changes in the

morphologic structure of the gland. However, the thyroid response to iodine is retained after hypophysectomy. Thyroidectomy appears to suppress F.S.H. in the male mouse pituitary.

Adrenals.—Hyperplasia of the adrenals is a prominent feature of the post-mortem findings in both acromegaly and pituitary basophilism. However, it is difficult to ascribe specific features of the respective clinical syndromes to the adrenal pathology. The similarity of the clinical pictures of pituitary basophilism and of certain adrenal cortical tumors would appear to be more than a mere coincidence. However, the most striking adrenal hyperplasia is found in conjunction with acidophilic rather than basophilic adenomas. There is a definite tendency toward the formation of adrenal cortical adenomas in both instances. Cytologic changes in the human anterior pituitary in adrenal insufficiency appear to involve a considerable reduction in the number of both acidophiles and basophiles, with the appearance of abnormal transitional basophiles.

The experimental work of Smith[82] demonstrated that adrenal cortical atrophy, following hypophysectomy, could be prevented by intramuscular implantation of fresh rat pituitaries. The pituitary is necessary for the compensatory hypertrophy of the remaining adrenal after unilateral adrenalectomy. The adrenocortical factor appears to be a separable fraction, distinct from the thyrotropic factor. The existence of a medullotropic factor has been suggested by Collip.[15] Recent developments suggest that pituitary basophilism may be differentiated from certain cases of masculinizing adrenal cortical tumors by the great increase in 17-ketosteroids in the latter. Castration is followed by a reduction in 17-ketosteroids.

Pancreas.—The high incidence of decreased sugar tolerance, glycosuria, and diabetes mellitus in both acromegaly and pituitary basophilism suggests the possibility of a direct effect of the anterior pituitary upon the islet tissue of the pancreas. Post-mortem findings in the pancreas of acromegalics have been equivocal; there are insufficient data to evaluate the state of the pancreas in pituitary basophilism. The results of cytologic studies of the anterior pituitary, following pancreatectomy or repeated injections of insulin, have been rather contradictory with respect to the nature of the cell changes, but consistent in implicating the acidophiles.

Experimental evidence begins with the demonstration by Houssay and Deulofeu,[43] that hypophysectomy increases the sensitivity to insulin and diminishes the severity of diabetes following pancreatectomy; that the reverse effects may be produced by administration of suitable anterior pituitary extracts, eventually leading to a diabetic state. Later, it was shown by Young[94] that a permanent diabetic state can be produced by repeated injections of appropriate anterior pituitary prepara-

tions, with consequent depletion of the cytoplasmic granules of the beta cells and hyaline replacement of the islets of Langerhans. The insulin content of such organs is much reduced but normal islet tissue may be restored by insulin treatment. There appears to be an early phase in the islet response to anterior pituitary extract during which the islet tissue and insulin content of the pancreas are increased. There is reason to suspect that the diabetogenic and pancreotropic principles are closely related to the growth-promoting factor of the anterior pituitary.

Thymus.—The frequent enlargement of the thymus in acromegaly is difficult to evaluate in view of the occasional thymic enlargement in chromophobe adenomas. Thymic atrophy appears to be the rule in basophilic adenomas.* Cytologic studies indicate that administration of thymus extract is followed by a definite increase in the percentage of pituitary acidophiles in young rats, especially males. Experimental evidence is somewhat conflicting but there is a suggestion that the thymus promotes growth and development. Administration of anterior pituitary extracts hastens thymic involution except in dwarf mice, where the anterior pituitary growth factor causes thymic proliferation. However, hypophysectomy accelerates involution of the thymus in young dogs or rats, but thymic hypertrophy may occur in adult rats. Atrophy of the thymus is produced by injections of testosterone proprionate or estrone, in rats, while hypertrophy follows castration.

Parathyroids.—The high incidence of skeletal decalcification in pituitary basophilism suggests the possibility of parathyroid involvement; in fact, parathyroid hyperplasia or adenoma formation were present in a significant number of cases. However, the few studies which have been reported on calcium and phosphorous balance[2] in pituitary basophilism have failed to reveal abnormalities as striking as those of hyperparathyroidism. Parathyroid hyperplasia or adenoma formation has been noted occasionally in acromegaly.

A study of the pituitary changes in male rats after parathyroidectomy or repeated injections of parathyroid hormone suggests that the former is followed by an increase in acidophiles, the latter by a decrease in these cells. Cytologic studies of the parathyroids in experimental animals suggest that parathyroid atrophy may follow hypophysectomy while hypertrophy of the grandules with hyperplasia of the chief cells has been reported after injections of anterior pituitary extracts. However, similar effects are produced by injections of pregnancy urine or estrone. Effects upon calcium levels are equivocal. Calcemia and hypercalcification of bones may be produced in some animals by estrogen; the bone changes are inhibited by testosterone.[35] It may be significant that estrogen has been reported to be decreased or absent in Cushing's disease, and the urinary androgens increased.[3]

Mammary Glands.—Occasional instances of persistent lactation have been reported in acromegaly; mammary hypoplasia is not infrequent

*Cushing's syndrome was present in 3 cases of thymic tumor (Table VI).

in patients with chromophobe adenomas. Experimental evidence indicates that a lactogenic factor, prolactin, may be obtained as a separable fraction from the anterior pituitary and is probably elaborated by the acidophiles. Both the hypophysis and thyroid hormone are necessary for lactation in mice. Estrogen apparently increases the amount of prolactin in the anterior pituitary of rats, but estrogens have been used to suppress or inhibit lactation in human acromegaly. The promotion of mammary duct growth appears to be a function of estrogen, although this effect is absent in hypophysectomized animals. The presence of a mammogenic hormone in the anterior pituitary has been suggested. Growth hormone may produce limited mammary development in hypophysectomized rats.

Metabolic Effects.—Clinical evidence of general metabolic effects is present in all types of pituitary adenomas. The excessive tissue growth of gigantism and acromegaly, the frequent gain in weight with a chromophobe adenoma, and the peculiar selective obesity of pituitary basophilism, all appear to be external manifestations of altered metabolic processes.

Effects upon carbohydrate metabolism have been recognized for some time; the decreased sugar tolerance and tendency toward diabetes in acromegaly, the increased sugar tolerance in chromophobe adenomas—both are familiar examples. Now it appears that basophilic adenomas are frequently associated with decreased sugar tolerance and occasional mild diabetes. The relation of these diabetic tendencies to the pancreas has already been discussed. However, there is evidence that the effect on carbohydrate metabolism is not limited to the islets of the pancreas but occurs in all tissues; the much-discussed insulin resistance of "pituitary diabetes" may be a clinical example of this. Experimental evidence concerning the relationship of the anterior pituitary to carbohydrate metabolism has been reviewed recently by Russell.[70] Hypophysectomized animals exhibit a rapid decline in blood sugar, depletion of liver and muscle glycogen, and elevation of respiratory quotient, when fasted. These effects may be prevented by administration of anterior pituitary extract (glycostatic effect), and are apparently due to acceleration of peripheral oxidation of carbohydrate. Hypersensitivity to insulin follows hypophysectomy while insulin resistance (glycotropic effect) may be produced by administration of suitable anterior pituitary extract. A ketogenic factor is also recognized in anterior pituitary extracts. Intermediate effects of the anterior pituitary through the thyroid appear to be limited to alteration of general metabolic rate and the rate of intestinal absorption of carbohydrate. The situation with respect to the adrenals is more complex but there is evidence for a synergistic effect between the anterior pituitary and adrenocortical hormones. In addition, it appears that while the anterior pituitary effect is chiefly repression of *peripheral* carbohydrate oxida-

tion and promotion of *muscle* glycogen deposition, the adrenocortical hormone exerts a similar effect in the liver. The gluconeogenetic action of anterior pituitary extracts appears to be mediated through the adrenal cortex. Hypergluconeogenesis has been suggested as a probable explanation for the alterations in carbohydrate and protein metabolism observed in Cushing's syndrome.[2]

Anterior pituitary effects on protein metabolism have been suspected in acromegaly and gigantism. The observation of decreased nitrogen excretion following administration of the growth factor adds experimental confirmation. Conversely, hypophysectomy is followed by increased nitrogen loss. Two mechanisms have been suggested by which the anterior pituitary may affect protein metabolism: (1) by direct action on muscles, stimulating protein catabolism; (2) by indirect action through the pancreas, stimulating protein anabolism. The first effect may be mediated through the thyroid, since thyroid administration has been shown to increase protein catabolism and nitrogen excretion. Alterations in protein metabolism may also be mediated through the adrenal cortex, since cortical hormone appears to influence the deamination of amino acids, the formation of carbohydrates from keto acids derived from amino acids, and the gluconeogenesis from endogenous protein; the net result is stimulation of protein catabolism. The observation of a negative nitrogen balance in certain patients with pituitary basophilism has been suggested to be explainable on the basis of an adrenocortical effect. Studies upon the specific dynamic action of protein indicate that this action is diminished by hypophysectomy.

Effects upon fat metabolism might be expected on the basis of the frequent clinical finding of obesity in cases of chromophobe adenoma and pituitary basophilism. However, in the former at least, the weight gain may be explained by the lowered basal metabolic rate. Experimental evidence is provided by the observations of increased peripheral fat and decreased liver fat after hypophysectomy.[71] Conversely, liver fat is increased and fat mobilization accelerated by anterior pituitary administration.

A specific metabolic principle in the pituitary has been suggested by Collip.[14] The elevation of basal metabolic rate of thyroidectomized an-

TABLE X

PROBABLE ENDOCRINE EFFECTS OF SPECIFIC PITUITARY CELL TYPES

EFFECT	ACIDOPHILES	BASOPHILES
Growth	+	
Gonads	+	+
Thyroid	+	?
Adrenals	+	+
Pancreas	+	
Thymus	?	
Parathyroids		?
Mammary glands	+	
Metabolic effects	+	+

imals by administration of crude pituitary extract, anterior lobe extract, or prolactin suggests the existence of such a metabolic principle. Administration of a potent preparation containing this principle is followed by a sharp elevation in basal metabolic rate and depression of the respiratory quotient. It has been suggested that this principle specifically stimulates the metabolism of fat. The metabolic principle is thought to have its origin in the pars intermedia of the pituitary.

Résumé.—Although further evidence is desirable concerning many of the effects ascribed to specific cells of the anterior pituitary, it is possible to give a tentative outline, based upon available information (Table X). Many of the symptoms of pituitary basophilism (skeletal decalcification, vascular hypertension, erythrocytosis, exophthalmos) await adequate explanation.

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OVARIAN TUMORS WITH SEX HORMONE FUNCTION

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DURING recent years there has been much interest among gynecologists concerning a group of ovarian tumors which have been shown to possess the property of producing the male or female sex hormone principles and thus to be capable of bringing about striking biologic effects. This functioning type of ovarian tumor is relatively rare, and the keen interest which this group has excited is due largely to the fact that gynecologists, endocrine-conscious as they have been for a good many years, must now include in the list of gynecologic endocrinopathies the syndromes produced by the small group of functioning ovarian tumors.

Even before we knew anything about sex hormones, certain ovarian tumors, like certain tumors of the adrenal, pituitary, and pineal bodies, had been related to certain abnormalities of sex characteristics, such as precocious puberty or virilism. But cases of this sort were reported as interesting but unexplainable anomalies, with no understanding of the mechanisms involved. We know little enough even now of the underlying mechanism in many disorders of this kind, but the newer knowledge of the sex hormones has made these various syndromes seem less mysterious than formerly and has actually made it possible to explain not a few of the manifestations quite adequately.

The concept that ovarian tumors can be functionally active was not as startling as it might have been had the same capabilities not already been demonstrated with tumors of other endocrine glands, notably the pituitary, and later the adrenal cortex, parathyroid, and pancreas. The older view that tumors are made up of parasitic cells which have cut themselves off from all functional activity except growth has been profoundly modified not only regarding endocrine factors, but also regarding external secretion. For example, the cells of certain hepatic carcinomas may produce bile, while mucin is produced by the cells of some intestinal carcinomas.

The forms of ovarian-functioning tumors with which we are concerned in this paper are all derived from cells dating back to the early developmental history of the ovary. Except for these, the only other variety of ovarian tumor which may in some cases assume functional properties is the relatively rare struma ovarii, or thyroid tissue tumor of the ovary. This represents a teratoma in which thyroid tissue overrides other alien elements, so that large parts of the tumor, or even

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its entire bulk, are made up of thyroid tissue. In a number of reported cases this tissue has become functionally hyperactive, producing clinical hyperthyroidism. This rare tumor type, however, need not be discussed in this communication. Those interested may be referred to the recent publication of Emge, wherein the subject is reviewed.

For an understanding of the special group of dysontogenetic functional tumors with which we are more directly concerned, some understanding of the early embryology of the gonads is indispensable. These organs are derived from a cell mass which develops in the anterior or ventral portion of the mesonephros. In the earliest stage of gonadal development it is not possible to distinguish whether the organ is to develop as a testis or an ovary. It is of interest to note that in this undifferentiated phase groups of cells may be segregated, and that from such cells tumors may arise in later life, regardless of whether the gonad develops into testis or ovary. In the ovary this tumor variety is now well recognized as the so-called dysgerminoma. The corresponding tumor in the testis is the well-known seminoma. Histologically these two tumor types are identical. As might be expected from their derivation, neither of these tumors possesses endocrine properties.

At a slightly later stage the cells in the sex gland anlage exhibit a differentiation into zigzag anastomosing tubules converging toward the hilum. In the case of the testis these cords are the progenitors of the seminiferous tubules, and by linking up with mesonephric tubular structures the entire testicular apparatus is soon laid down, the Wolffian duct itself becoming the vas deferens. From our own immediate viewpoint, however, it is important to remember that in the ovary as well as the testis the same sex cord differentiation takes places, though in the ovary it is abortive and incomplete, and is soon followed, with overlapping, by a second differentiating process. To put it very figuratively, the second or feminine differentiation takes place over the fossil remains of the first or more characteristically male process. It is believed that in the fully developed ovary of later life vestiges of these originally male-directed cells may persist in its medullary portion and that it is from such potentially masculine cells that tumors may arise which in their structure exhibit some degree or other of testicular architecture and which have the capacity of producing the male sex hormone.

To this group the designation of arrhenoblastoma was given by Meyer, to whom we are indebted for much of our knowledge of this whole special group of ovarian tumors. The explanation given of the histogenesis of arrhenoblastoma, as throwing light upon their masculinizing effect, will probably have to be modified as our knowledge of sex differentiation increases. The possible role of organizers and determiners of sex in the ovarian cortex and medulla is now being stressed by

biologists and cannot be overlooked. Moreover, the intimate embryologic relationship of the adrenal cortex and the ovarian medulla make it easy to understand that certain adrenal cortical tumors, like the ovarian arrhenoblastoma, have masculinizing tendencies, and some investigators have suggested that the embryologic inclusion of testicular elements in the adrenal area may explain the masculinizing property of certain tumors of the adrenal.

On the other hand, it is of interest to note that tumors made up of adrenal tissue may occur in the ovary and that such tumors produce a masculinization syndrome quite indistinguishable from that of arrhenoblastoma. The intensive studies of the past two or three years have shown that both male and female sex hormones are produced in the adrenal cortex, and interesting relationships between these and desoxycorticosterone have been demonstrated, but we are still in the dark as to the exact nature of the corticogonadal mechanism which is so clearly important in the differentiation of sex characters.

With the appearance of the typical feminine differentiating processes in the ovary, the primitive follicular apparatus is soon formed by the clusterlike grouping of granulosal cells around the oögonia. According to Meyer, rests of redundant granulosa may be left over and from them may later arise the well-known granulosa cell tumors. Since the cells from which they arise have been predestined as feminine, it is not surprising that such tumors are feminizing in their effects through their production of the estrogenic hormone. Here again, evidence is accumulating to indicate that Meyer's original concept must be modified. There is increasing opinion that both granulosa and theca cells arise from differentiation in situ of the ovarian mesenchyme and that the derivation of the feminizing group of tumors must be traced back to a mesenchymal, that is, a progranulosal and prothecal, stage. Such tumors may therefore assume epithelial (granulosal) characteristics or histologically they may appear to be stromal (thecal) in character. To the former group the designation of granulosa cell carcinoma is applied; to the latter, thecoma. Acceptance of such a view makes it difficult to separate these two varieties of tumor as sharply as has been done by some authors. Indeed, it is common to find an intermingling of granulosal and thecal elements in one and the same tumor.

In either the granulosal or thecal tumor luteinization changes may take place, probably through an excitation of the same sequential pituitary effect exhibited in the conversion of the normal granulosa of the reproductive epoch into lutein cells. The luteinization changes in the tumors may be partial, constituting the so-called folliculome lipidique described first by Lecéne, or they may involve the whole structure of granulosal tumors, which, in such cases, are usually of small size. Thus is produced the so-called luteoma. Concerning the latter tumor type there is still much discussion and uncertainty, chiefly because of the

difficulty in certain cases of determining whether a given tumor is of lutein or adrenal character. A number of instances have been recorded in which luteoma is said to have brought about masculinization phenomena, but the probabilities are that most of these have really been of adrenal nature. However, in view of recent experimental investigations which indicate that progesterone may actually produce certain masculinization phenomena, such an assumption cannot be taken for granted. This aspect of the general subject is still quite confused. For a fuller discussion on this point the reader may be referred to the recent article of Rottino and McGrath, who propose for this group of tumors of uncertain histogenesis the designation of masculinovoblastoma.

Pathology.—The feminizing tumors are characterized by marked individual variation in histologic pattern. The granulosal group, however, is usually readily distinguishable by the granulosal morphology of the constituent epithelial cells together with certain growth characteristics which appear to distinguish granulosal cells in general. Among these is a tendency to an arrangement in small clusters suggesting the appearance of the primitive follicles of the ovary, except for the inclusion of the germ cells, and also the tendency to form tiny areas of cystic liquefaction resembling the Call-Exner bodies seen in the granulosa of many species, especially the rodents.

The granulosal tissue may be quite diffuse, but more frequently it is divided by trabeculae of connective tissue into long columns, producing a cylindromatous pattern. Much less frequent is an arrangement in spherical masses, the centers of which often exhibit cystic degeneration, so that there is at least a superficial resemblance to large follicles. This so-called von Kahlden type was therefore formerly often spoken of as folliculoma malignum. Still other variations occur, such as the gyriform and the pseudoadenomatous.

Grossly granulosa cell tumors may be of minute size or they may reach very large proportions. The smaller ones are apt to be solid, but those of larger size commonly show one or more cystic cavities due to liquefaction changes. The substance of the tumor, as revealed on cross section, is of grayish granular appearance with often areas of yellowish hue. The thecomas as a group are apt to be of more moderate size and of fibromatous appearance, although softer areas and small cystic cavities may likewise be noted.

There is much more difficulty in describing the pathology of arrhenoblastoma, which includes a whole series of gradations, from highly differentiated testicular tissue at one extreme to tumors so undifferentiated that only close study will reveal the sex cordlike cell arrangement that may constitute the only clue to their real nature. It is here that a knowledge of early gonadal embryology will stand the pathologist in good stead. Meyer has distinguished three varieties. The

highly differentiated type corresponds to the so-called testicular adenoma, originally described by Pick. Between this and the very undifferentiated variety falls the intermediate type, in which one always finds a tendency to tubule arrangement, representing abortive efforts at reproducing the testicular tubules. Other testicular characteristics, such as rete elements or groups of cells resembling the interstitial cells of Leydig, are found in a considerable proportion of cases.

Grossly the arrhenoblastoma is almost always a solid tumor of small or moderate size, although in some cases the growths have been very large, even to the size of a man's head. The cut surface is fairly firm and of grayish color, often with areas of yellowish tint, and sometimes of reddish, hemorrhagic appearance. As a result of secondary degenerative changes, cystic cavities of considerable size may be formed.

Malignancy.—The general statement may be made that while both granulosa cell carcinoma and arrhenoblastoma are undoubtedly much less malignant than the more common types of ovarian carcinoma, they are always to be looked upon as potentially malignant, and in many individual cases the degree of clinical malignancy is high. It is, of course, true that in many instances such neoplasms have seemed to run a benign course with no recurrence after unilateral removal of the adnexa. This has been particularly true in young children, perhaps because at this age the endocrine symptoms produced by such tumors are more striking than in later life, leading to their early recognition.

On the other hand, other members of this tumor group have been highly malignant, with rapid recurrence even after radical operations. Moreover, recurrence has sometimes been very late, after intervals of ten or even eighteen years. Only a few follow-up studies have been made, but I believe that the 28.1 per cent recurrence rate revealed in the series reported by Novak and Brawner would give a fair estimate of the degree of malignancy of the general group, although some authors put it much lower. In any event there does not seem any justification for the rather light attitude exhibited by some writers toward this type of tumor, especially since histologic criteria have not been found to constitute a reliable index of the degree of malignancy.

Still less certain are we as to the exact degree of malignancy of arrhenoblastoma. Only a few more than sixty cases have thus far been recorded, and most of these, because of the biologic interest of the tumors, have been reported soon after observation, too soon to permit of any statement as to the ultimate result. That they may recur after removal is shown in the cases of Novak and Long, Meyer, Kleinhans, von Szathmary and Taylor, and Wolfermann and Kroek. On the other hand, as with granulosa cell carcinoma, a considerably larger group of patients has apparently been cured by conservative operations.

ENDOCRINE EFFECTS

Feminizing Group.—Bearing in mind the estrogen-producing function of this group of tumors, it is easy to understand their biologic effects. The latter, as might be expected, will differ according to the age period at which such tumors develop.

When such growths arise in young children, as they sometimes do, their effects are what one would expect from the production of large amounts of estrogen long before the age of puberty. The characteristic secondary sex characteristics which appear normally at the pubertal epoch are due to the awakening estrogenic function which occurs at that time. When the organism is subjected to the estrogen stimulation of granulosal tumors abnormally early, one would expect evidences of precocious puberty, and this is exactly what occurs. Premature menstruation, premature hypertrophy of the breasts, and axillary and genital hairgrowth are the most conspicuous symptoms. The periodic bleeding is not associated with ovulation, in which respect it differs from that seen with precocious puberty due to certain extraovarian factors. Removal of the tumor is followed by prompt regression of the precocious symptoms, this constituting a clear-cut demonstration of the causal role of the tumor in the production of the syndrome.

During menstrual life, the ovaries normally produce considerable quantities of estrogen, and the secondary sex characters are already fully developed. The effects of estrogen-producing tumors in such women are therefore merely quantitative, the chief effects being on the menstrual function. Even these may not be notable, as we know that a relative hyperestrogenism is not invariably associated with menstrual excess. While the latter often occurs, menstruation may be quite normal or it may even be absent for many months at a time.

The uterus retains its sensitivity to estrogen long after the menopause, so that feminizing tumors in postmenopausal patients bring about varying degrees of increase in size of that organ above that of the usual senile uterus. Moreover, the uterine mucosa characteristically exhibits a hyperplasia, while periodic bleeding is likely to occur, simulating a re-establishment of menstruation. As in the prepubertal group, this is of the anovulatory, estrogen-induced type. The breasts of the senile women have lost their reactivity to estrogen, so that breast changes are not noted.

Masculinizing Group.—The production of androgenic principles by the masculinizing tumors brings about a sequence of endocrine effects which is divisible into two phases. The first of these consists in the appearance of certain symptoms which are not in themselves masculinizing but which represent a subtraction of certain features from the typically feminine complex. Among these symptoms are amenorrhea,

retrogression of the breasts, and sometimes a loss of the subcutaneous fat which gives the female figure its typical rounded contour. This defeminization phase is followed by the appearance of certain phenomena which are to be looked upon as definitely masculinizing. Chief among these are the appearance of a hairy growth on the face and other parts of the body, hypertrophy of the clitoris, and deepening of the voice. This is the sequence to be expected in the characteristic case, although there are all sorts of variations in degree.

As a matter of fact, there are some tumors which undoubtedly belong in this pathologic category but which produce little or no endocrine effect. In some cases this is explained by the very small size of the growths, while in other cases the explanation is uncertain and speculative. Removal of the tumor is followed by regression of the abnormal phenomena, although this is not always as complete and prompt as with the feminizing group. The defeminization phenomena disappear promptly and completely, but the genuinely masculinizing signs regress much more slowly and sometimes incompletely.

Diagnosis.—From what has been said it is evident that the preoperative diagnosis of granulosa cell carcinoma during menstrual life is rarely, if ever, possible, as it does not ordinarily give rise to symptoms different from other types of ovarian tumor. On the other hand, when an ovarian tumor is demonstrated in a child who exhibits the clinical phenomena of precocious puberty, it is reasonably certain to be of the granulosal type. It should not be forgotten, however, that certain other causes of precocious puberty are more frequent than this, and unless a tumor is palpable operation is not usually justified. That this is not an unnecessary admonition I know from personal knowledge of a number of cases in which ovaries have been removed merely on the suspicion that they may harbor small granulosa cell tumors. In patients of this early age group the demonstration of considerable quantities of estrogen in the urine would be suggestive but not conclusive, as the same finding might be noted in patients in whom an extraovarian factor is responsible for the precocious appearance of menstruation and other pubertal phenomena.

In the postmenopausal group, the association of periodic bleeding with an ovarian neoplasm, especially when the uterus is well above the senile size, should make one suspect granulosa cell carcinoma. Diagnostic curettage in such cases is likely to show a hyperplastic rather than atrophic endometrium. However, it is to be remembered that postmenopausal hyperplasia of the endometrium occasionally occurs in the entire absence of any tumor, just as estrogen may be found in the urine of some women long after the menopause. However, a judicious weighing of such evidence will permit of at least a strongly presumptive diagnosis in some cases.

As to arrhenoblastoma, the demonstration of a definite solid ovarian tumor in a woman previously normal and then developing defemini-

zation phenomena, followed soon by hirsutism, clitoris hypertrophy, and voice changes permits one to make a presumptive diagnosis of masculinizing tumor. This would usually prove to be arrhenoblastoma but rarely might be the adrenal type of ovarian tumor, which gives rise to identical symptoms. Here again a word of caution is necessary. The finding of a tumor in a woman who shows hypertrichosis, flat breasts, a rather deep voice, and perhaps amenorrhea does not justify any worth-while suspicion of arrhenoblastoma if the secondary sex abnormalities date from puberty, as they so often do. In such cases the evidences of mild intersexuality are almost always of the congenital or chromosomal type. Any associated ovarian tumor is likely, therefore, to be purely coincidental, and operation will usually reveal one of the ordinary tumor types, such as cystadenoma. When, however, the abnormal symptoms develop rather abruptly in women who previously have been typically feminine, the finding of an ovarian tumor is much more significant. Sex hormone studies have not yet proved of any great value as a help in the diagnosis of this group of tumors.

Treatment.—The treatment of the tumors of this entire group is surgical, but a word as to the extent of the operation seems necessary. Certainly in young individuals, in whom it is obviously highly important to preserve reproductive function, the operation should be a conservative one. In cases of this group, especially in children, the tumor is usually small and unilateral, and removal of the adnexa of the diseased side is ordinarily indicated. Postoperative radiotherapy would obviously be contraindicated, as in itself it might result in sterilization of the patient. The importance of postoperative follow-up need hardly be stressed in view of the potentialities of such tumors.

When such tumors are encountered in older women, as is true of the largest proportion, conservative operation would seem unwise. As a matter of fact, the real nature of granulosa cell carcinoma is often not suspected at the operating table, especially by the surgeon untrained in pathology. It is likely to be mistaken for ovarian carcinoma of the more ordinary types, so that complete removal of the uterus and adnexa is done, or should be done, whenever possible. While the results in the functioning group of tumors are in the main much better than with ovarian carcinoma in general, recurrences are sufficiently frequent to indicate the malignant potentialities of this entire group and to contraindicate any attempt at conservatism except under the conditions emphasized in the previous paragraph.

Opinions still differ as to the value of postoperative radiation where radical operation has been done, although most surgeons will probably prefer to employ this extra measure with these tumors as with other forms of malignant ovarian tumors. There are undoubtedly some members of this special tumor family, especially some cases of granu-

losa cell carcinoma, which are relatively radiosensitive, although even rapid recurrence may in other cases occur even if radical operation has been followed by radiation.

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ENDOCRINE FACTORS IN THE ORIGIN OF TUMORS OF THE UTERUS

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THEORIES on the causes of all tumors, perhaps especially those of the reproductive organs, have undergone a radical revision in the last ten or fifteen years. Prior to that time chief emphasis was placed upon trauma or chronic irritation with the hypothesis of the special predisposition of displaced embryonal rests to be used when other explanations were lacking. Carcinoma of the cervix was generally regarded as arising on the basis of chronic inflammatory lesions developing in lacerations sustained during childbirth. Cancer of the breast was assigned sometimes to trauma, sometimes to the irritating effects of undischarged secretion. Cancer of the endometrium was given little consideration but was somewhat loosely referred to senile endometritis. The embryonal theory on the other hand was of value in explaining certain complicated new growths, especially of the adenomyoma group, but fibroids and some ovarian tumors were also often laid to the persistence and late development of various embryonic structures. These factors are not yet to be excluded, but they have been relegated to the background to give place to the study of specific chemical stimuli, particularly those of hormonal character.

Although recent progress toward the establishment of the hormones as a factor in tumor genesis has been chiefly in the hands of laboratory workers, it must not be supposed that their work was the actual beginning. Intimations that endocrine factors were concerned in the origin of pelvic tumors date relatively far back in modern gynecologic history. Sixty years ago Brennecke[6] recognized a hyperplastic condition of the endometrium and correctly ascribed it to disturbances in ovulation and corpus luteum formation, a point amply confirmed and widely accepted by gynecologists many years before the hormones of the ovary had been isolated. The relationship of the uterine fibromyoma to the ovary has also been carefully considered by several generations of clinical gynecologists and since Hegar's[29] article of 1887, there has been an almost unbroken series of reported observations on the nature of the ovarian lesion associated with this tumor.

The experimental period in the investigation of these relationships was initiated by several fundamental discoveries in the fields of biology and chemistry. Of primary importance was the Allen-Doisy test which made possible the measurements of estrogenic activity. Of equal value was the isolation and eventual synthesis of many of the sex

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hormones in pure form. With these instruments for research and the successful breeding of strains of mice with a hereditary cancer of the mammary gland, the development of a new field in the investigation of reproductory tract tumors was ready to commence.

Work on the experimental production of animal tumors by means of hormones has produced a great body of literature which has been adequately reviewed elsewhere.[2, 19, 78] As a result of these investigations a number of neoplasms are now readily produced in several species of animals which are similar in their microscopic structure to many of the common spontaneously occurring human tumors. Perhaps the principal problem of the moment is to find satisfactory evidence that in women with tumors of these types hormone conditions have been present which in some way resemble those that must be artificially created to produce the experimental tumors in animals.

Methods of studying ovarian function in human beings are still imperfect and clinical evidence of a hormone disorder associated with a developing tumor is indirect and difficult to evaluate. Briefly such evidence may be classified under several headings.

1. The clinical history has for years led to inferences in regard to the origin of tumors. The relation to previous pregnancies or to sterility, records of past menstrual disturbances or of anomalies of puberty or the menopause are all data which can be statistically handled and must be taken into account.

2. Histologic or pathologic study of various parts of the reproductive organs may yield information of value. The ovaries themselves may contain follicle cysts or a granulosa cell tumor as an acceptable source of the estrogens which produced the tumor. The endometrium on the other hand may be looked upon as a sensitive indicator of sex endocrine function and its status in a patient with a reproductive tract tumor will indicate whether, at the moment at least, the ovarian function is normal. Finally a tendency to the association of several tumors in the reproductive tract of the same individual is of interest, for it indicates either a general predisposition or a type of stimulus having a widespread effectiveness, as might be expected from a hormone as a factor in tumor development.

3. Clinical therapy has made some contributions to the solution of the problem. The fact that many of the benign reproductory tract tumors tended to shrink or even disappear after bilateral oophorectomy has long been known and accepted as proof that substances formed in the ovary were, if not the cause of the tumor, at least essential in maintaining the continued susceptibility of the organs to tumor formation. More recently there have been some reports indicating that the administration of various hormone substances, the estrogens, progesterone or testosterone, might accelerate or modify the growth of neoplasms in the female pelvic organs.

4. Finally, evidence to solve this problem has been sought in the excretion rates of various products of the sex endocrine organs. These studies have been interesting but have led to limited conclusions. The rate of urinary excretion of an estrogen, for example, may have a very remote relationship to its rate of formation or of its utilization by specific tissues. Nor does the estrogen excretion in a patient with a fully developed tumor give much indication of the conditions under which tumor growth was initiated, perhaps years before.

Evidence such as this is all that is available to the clinician to check the suggestions made to him by the animal experimenter. In the following pages the principal tumors produced by hormonal agents in the uterus of various laboratory animals will be considered in relation to the morphologically similar tumors in women and the reasons given for believing that the causes of these tumors may also be similar.

Endometrial Hyperplasia.—Hyperplasia of the endometrium has become a clinical entity accepted by most gynecologists. The histologic picture, with the glands of irregular size lined by nonsecreting epithelium, is fairly characteristic although extreme forms may range from those which are difficult to distinguish from normal proliferating endometrium on the one hand to those suggestive of early adenocarcinoma on the other.

The typical histologic pattern of endometrial hyperplasia has been produced in all of the common laboratory animals by the simple injection of various estrogenic compounds.[8, 85-87, 89] Evidence is accumulating, however, that a great excess in estrogenic stimulation is not the essential factor in the cause of the disease, but rather a continuity of estrogenic stimulation without the periods of rest afforded by the normal estrus cycle. The development of the disease is also favored by the absence of the usual balancing effect of the corpus luteum. The relationship of endometrial hyperplasia to disturbed rather than simple excessive ovarian function is made especially evident by studies of Lipschütz[42, 43] on the effect of partial oophorectomy in the guinea pig. He found that an imbalance resulted when the residual fragment of ovary underwent a compensatory hypertrophy of the follicles with incomplete or absent corpus luteum development, and in animals so treated there developed numerous signs of atypical tissue proliferations among which hyperplasia of the endometrium was prominent. Hyperplasia has also been reported to follow the disturbances of ovarian function resulting from the irradiation of the ovaries by x-rays[69] and by the implantation of testicular tissue.[63] The protective effect of the corpus luteum is shown by the reports of several writers that hyperplasia is more difficult to produce by means of an estrogen if the animal's own ovaries are not first removed[53] or if progesterone is simultaneously administered.[55]

The evidence that hyperplasia of the endometrium as it occurs in women has the same cause as the experimentally produced animal lesion is quite convincing. Schroeder,[70] in 1915, published his work ascribing the disease to the persistence and prolonged action of an unruptured Graafian follicle on the endometrium, basing his theory on a series of cases in which he found a large follicle in the ovary and no recent corpus luteum. The condition of the ovaries in cases of hyperplasia has been the object of numerous investigations since that time, all tending to confirm the view that the disease results from prolonged follicular activity without normal corpus luteum formation.

Interesting support of this relationship is found in cases of certain ovarian tumors. Both granulosa- and theca-cell tumors of the ovary manufacture estrogenic material which can be detected in the urine in large quantities. As is well known, uterine bleeding from a hyperplastic endometrium is a common symptom of this type of tumor.

Efforts to demonstrate excessive quantities of estrogenic substance in the urine of patients with this disease have in general indicated an increased excretion of the hormone.[16, 39, 74, 83] Investigations on this subject were carried on during the earlier days of urinary hormone studies, however, and there appears to be a real opportunity for detailed study of steroid excretion in such cases with the utilization of more modern techniques.

The observed effects of treatment also tend to confirm the endocrine nature of this disease. Castration is invariably curative, a fact which makes very successful the radium or x-ray treatment of women with benign vaginal bleeding at the time of the menopause. Furthermore, the administration of very large doses of an estrogen, 600,000 international units, may be followed by the production of an experimental hyperplasia in women, histologically similar to the spontaneous disease.[87] Consistent with the previously noted facts on the etiology of the disease is the observation that progesterone in large doses has a curative effect.[72]

One somewhat confusing point has arisen with the observation of cases of hyperplasia developing some years after the menopause.[5, 57, 80] Various hypotheses have been offered as to the source of the estrogens which might produce the lesion late in life. At present the estrogenic origin of the proliferative changes in the senile endometrium must be held in some doubt.

The origin of the cystic hyperplasia of the human endometrium on the basis of a dysfunction of the ovary, resulting in what may be characterized as a persistent, unopposed action of estrogen, may be regarded as established. This being true, the finding of endometrial hyperplasia in association with another reproductive tract tumor is at least presumptive evidence that the estrogens play some part in the origin of the other tumor also. This reasoning has been used to relate a considerable list of pelvic tumors to an ovarian hyperfunction.

Squamous Metaplasia of the Endometrium.—In a number of animal experiments the transformation of portions of the endometrium into a stratified squamous epithelium has been reported as an estrogen effect.[40, 48, 73] Lipschütz[43] also observed this in guinea pigs after partial oophorectomy.

Islands of squamous epithelium are well known to occur in the human endometrium (Fig. 1) and are perhaps the counterpart of the squamous metaplasia developing in animals after estrogens. Such metaplasia is a not uncommon associated finding in cases of endometrial hyperplasia,[33] a point giving a little support to the estrogenic view of its origin.

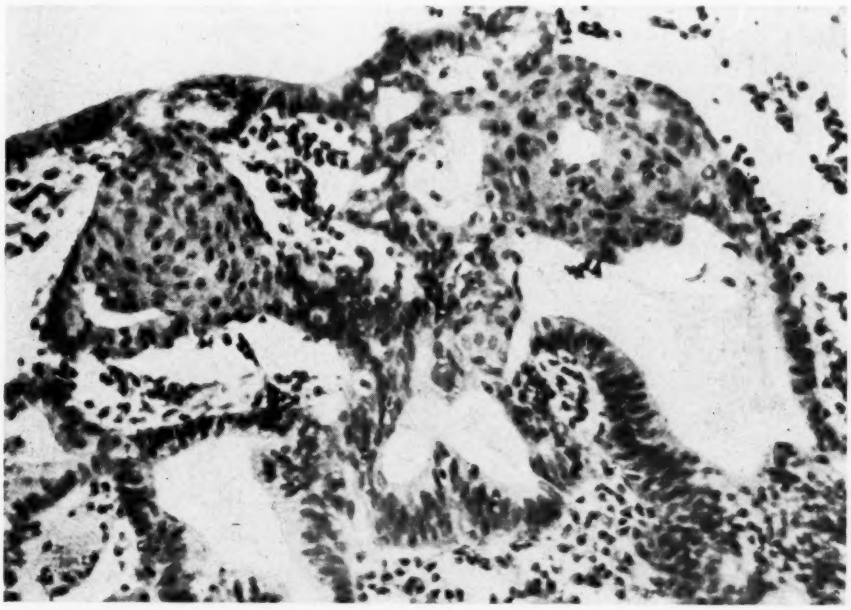

Fig. 1.—Squamous metaplasia of the endometrium with adenocarcinoma.

Carcinoma of the Endometrium.—Although no tissue would appear to be more susceptible to the action of the estrogens, tumors of the endometrium have rarely been reported in laboratory animals after estrogen injections. Those which have developed seem to have only a remote morphologic relationship to the carcinoma of the corpus uteri in women.[41, 64]

Spontaneously developing tumors of the rabbit endometrium have, however, been described and arise under circumstances which give a new direction to thought on the nature of the endocrine factor in carcinogenesis. These "adenomata" arise multicentrically in the glandular mucosa of relatively old animals and spread by both local extension and metastasis.[27] Their appearance is associated with certain changes in the adrenals, thyroid, ovaries, and mammary glands which are some-

what similar to the effects produced by estrogen injection. Of particular interest was Greene's observation that tumors occurred in animals that had previously suffered from mild attacks of "toxemia of pregnancy," which he felt may have caused damage to the liver and a relative incapacity to inactivate estrogens.[26] This mechanism, if correct, would implicate the liver as a possible cause of many excessive estrogen effects.

The evidence for an estrogenic factor in the origin of endometrial cancer in women is confusing. From a clinical standpoint, it is noteworthy that the disease has a slight tendency to favor nulliparous women and it has been reported to have a special predilection for women with a delayed menopause.[9] Both of these trends suggest an endocrine factor.

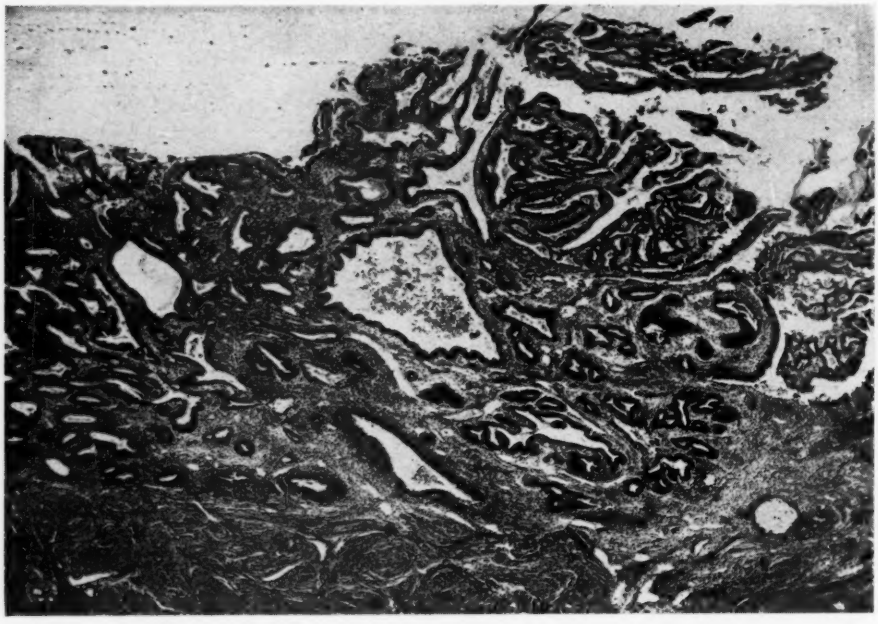

Fig. 2.—Adenocarcinoma associated with hyperplasia of the endometrium in a patient 48 years of age.

The relationship of carcinoma to hyperplasia of the endometrium is an important and disputed point. Certainly only a very small proportion of the cases of the very common hyperplastic lesion can go on to develop into the relatively rare cancer of the corpus uteri. Follow-up studies of cases of endometrial hyperplasia have in fact yielded few examples of later development of cancer.[34, 49]

Pathologic specimens in which carcinoma is found arising in a hyperplastic endometrium are not uncommon according to certain observers,[58, 77] whereas others insist that the association is no more than accidental.[15, 38, 62] Herrell[31] denies that hyperplasia is commonly found

with corpus carcinoma, but notes instead that in 96 per cent of the 50 cases he studied there was a "persistent proliferative type of endometrium." This he regarded as due to the "unopposed action of the follicular hormone." Jones and Brewer,[38] in a study of 68 patients with corpus cancer, found only 2 with cystic hyperplasia and concluded that there was no evidence for the "unopposed action" of estrin in the production of endometrial cancer. These wide differences of opinion must evidently be due in part to a lack of agreement as to what constitutes hyperplasia of the endometrium in the postmenopausal woman, the type of patient in which cancer of the endometrium usually occurs.

An example of the association of hyperplasia and adenocarcinoma of the uterus is shown in Fig. 2. It is of interest that in this case another lesion, in which an estrogenic factor must likewise be considered, namely, adenomyosis of the uterus, was also present (Fig. 3).

Fig. 3.—Adenocarcinoma associated with adenomyosis in the patient shown in Fig. 2.

While this controversy continues, another group of cases is beginning to be reported which may constitute the most important evidence for an estrogen factor in endometrial cancer. These belong to the steadily increasing list of patients who have been observed with an association of a granulosa cell tumor of the ovary with an adenocarcinoma of the endometrium. Apparently the first of these was described by Schroeder,[71] in 1922, but recently there have been reports of several, notably 3 by Dockerty,[11] 3 by Stohr,[75] 1 by Russell,[67] and 1 by Taylor and Greeley.[79] Another possibly similar case has recently been observed at the Memorial Hospital and is illustrated in Figs. 4 and 5. Two cases are also on record of carcinoma of the endometrium in association with theca-cell tumors of the ovary.[11, 66] In view of the relative

rarity of these ovarian tumors it is scarcely conceivable that the association with endometrial cancer was mere accident. With the estrin-producing capacity of the granulosa-cell and theca-cell tumors in mind, it is difficult to deny the probable sequence of hyperestrinism, hyper-

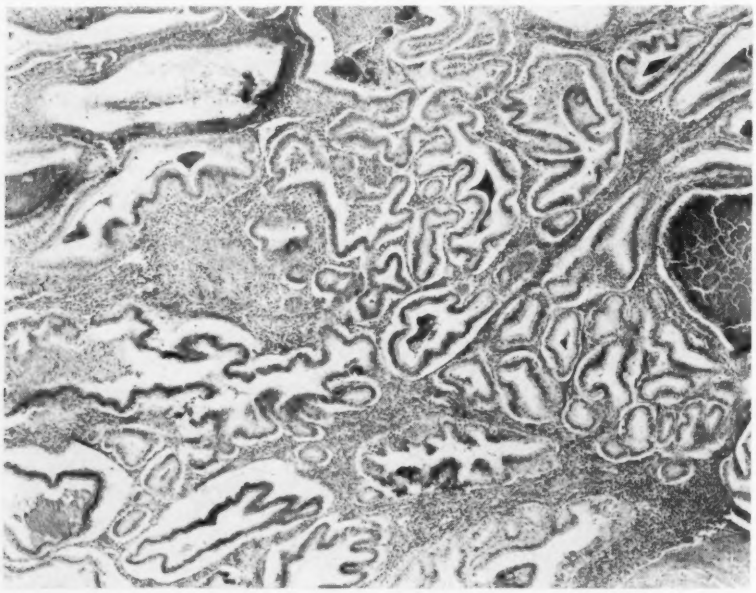

Fig. 4.—Adenocarcinoma or hyperplasia of endometrium in uterus of 65-year-old woman with granulosa-cell tumor.

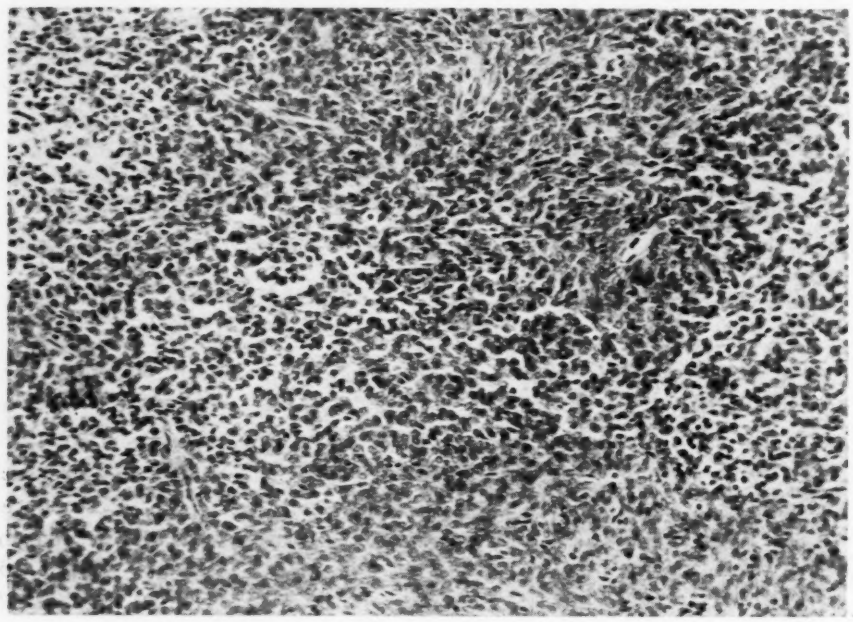

Fig. 5.—Granulosa-cell tumor in patient whose endometrium is shown in Fig. 4.

plasia of the senile endometrium, and cancer in at least this special group.

Fibromyoma Uteri.—The attempts to produce tumors of the smooth muscle of the uterus illustrate very well the presence of factors of susceptibility inherent in the species, race, or individual in addition to some precipitating cause such as an endocrine stimulus. The prodigious number of mice, rats, and rabbits injected with various estrogens failed to yield any convincing myomas of the uterus. Injections of estrogens into guinea pigs led immediately to fibromatous tumors, not only of the myometrium but of subperitoneal tissues throughout the abdominal cavity. Although the production of these tumors was first reported by Nelson,[54] the detailed study of these growths and the special conditions underlying their appearance have been made by Lipschütz and his co-workers in Chile.[44-47]

The estrogen-produced tumors of the guinea pig are fibromas with some smooth muscle fibers, arising perhaps by proliferation of the celomic endothelium.[47] Tumors appear on the uterus, but also on the surface of the liver, stomach, intestine, parietal peritoneum, and undersurface of the diaphragm.[44] Various estrogens will result in these tumors but an esterified compound, such as estradiol benzoate, appears to be the most effective, perhaps because with this the estrogen effect is most continuous. Discontinuous treatments, even if carried on over a long period of time and with large doses, may fail to produce tumors,[45] and their appearance may be prevented by combining progesterone or testosterone propionate with the estrogen injections.[46] The conditions governing the production of these tumors follow the rule noted before for hyperplasia of the endometrium, namely, that stimulation should be continuous and not balanced by the moderating effect of the corpus luteum.

Corroborating evidence that the fibromyomas in the human being are due to the estrogens is diverse and controversial. Pathologic changes in the ovaries of women with fibroids have been discussed for at least fifty years with little progress being made, perhaps because of our meager knowledge of the morphologic basis of ovarian dysfunctions. In recent years Witherspoon[82] particularly has stressed the association of follicular cysts with fibroids and on the basis of his observations has built up a theory of hyperestrinism as the cause of these tumors. Two very careful studies[7, 28] deny that cystic changes occur with any unusual frequency. Brewer and Jones[7] in particular have recently studied the ovaries in a series of 100 patients with fibromyoma and report that ovulation and corpus luteum formation were found in the frequency to be expected in normal women.

The disagreement as to the endometrial patterns in patients with fibroids parallels that in regard to the state of the ovaries. Witherspoon[82] found that hyperplasia of the endometrium was frequently

associated with uterine fibroids and reported a series of 44 women originally found to have only endometrial hyperplasia who subsequently developed fibroids. He believed that hyperestrinism was the common cause of hyperplasia of the endometrium and of fibroids, the former developing when the causative factors were operative over a short period, the latter when over a longer period. Against this extreme view may again be cited the work of Brewer and Jones[7] who in their series of 100 fibroids found only one example of hyperplasia and that of moderate degree.

A particular opponent of an ovarian dysfunction as the cause of fibroids is Robert Meyer,[51] who pointed out that many women with fibroids undergo normal cyclical changes in the endometrium, menstruate regularly, and even become pregnant. Some dependence upon the ovary is of course evident because of the shrinkage in the size of the tumor after the menopause. This may occur through the intermediation of the blood supply, however, and fibroids with extensive vascular adhesions to extra pelvic abdominal organs may continue to grow after the menopause in spite of atrophy of ovaries and uterus.[10]

More direct studies of the estrogens in relation to fibroid growth in women have met with little success. High concentrations of estrogenic substances in the tumors themselves have been reported, but these observations are now largely discredited. The excretion of estrogenic and androgenic substances in the urine of women with fibroids appears to be normal.[18]

The case for a hormone factor in the etiology of fibroids in women still seems to rest chiefly on the atrophy that undoubtedly results from removal or destruction of ovarian function. To this may perhaps be added the support afforded by the experimental production of allied, but perhaps not strictly analogous, tumors in the guinea pig.

Adenomyosis Uteri.—The active penetration of the myometrium by glands from the basal layers of the endometrium is another lesion which apparently develops only during years of active ovarian function. Formerly regarded as inflammatory and termed adenomyositis, it has gradually come to be regarded as in some sense an endocrine induced disease, resulting either from a lost resistance of the endometrium or an increased capacity for regeneration of the basal layers.[52]

Experimental production of adenomyosis has been little considered, perhaps because the preclinical workers are scarcely conscious of the lesion. Penetration of the muscularis by endometrial glands has been observed after estrogens, however, and is beautifully illustrated in the work of Lipschütz in which he produced various types of genital hyperplasia in guinea pigs by partial oophorectomy.[43] The only clinical evidence that has been offered for the ovarian origin of adenomyosis of the uterine wall has been that afforded by the association of other lesions, in particular pathologic changes in the ovaries,[1, 37] granulosa-cell tumor of the ovary,[81] and hyperplasia of the endometrium.[37, 56]

The patient, microphotographs of whose uterus are shown in Figs. 2 and 3, is illustrative of this point.

Squamous Metaplasia and Precancerous Lesions of the Cervix.—Transformation of the columnar cells of the cervix into a stratified squamous epithelium is a commonly observed sequel to estrogen injections in many animal species. The first report on the production of such lesions in the monkey was made by Overholser and Allen[60] who at first believed that the lesion produced was actually beginning carcinoma, but subsequent work has shown that these estrogen-produced lesions of the cervix in the monkey and most animal species are not malignant.[12, 30, 35, 61, 88] The structures produced do, however, closely resemble lesions familiar to the gynecologist as leucoplakia and squamous metaplasia or epidermidalization of the cervical glands.

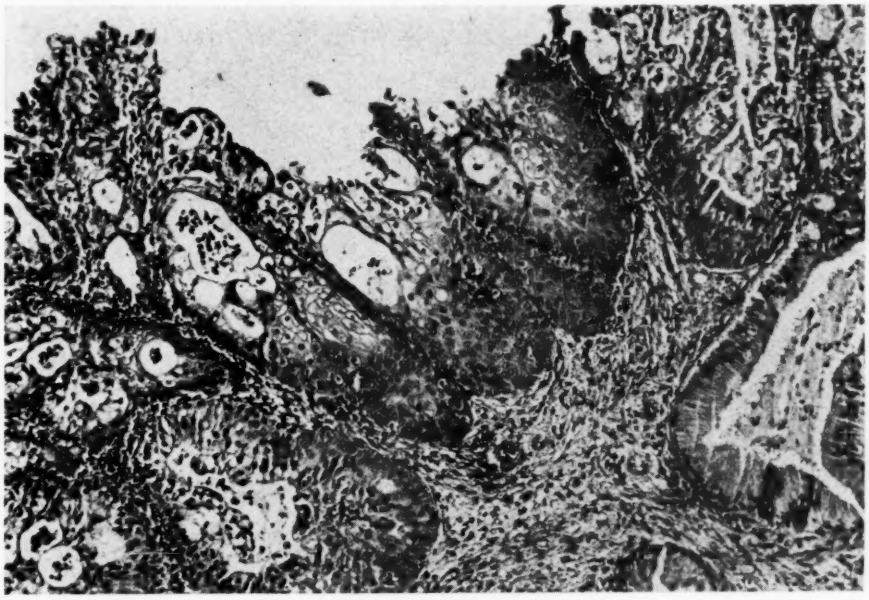

Fig. 6.—Squamous metaplasia of columnar epithelium in a cervical polyp.

Evidence from human material that such lesions are estrogenic in origin is largely lacking. Squamous metaplasia of the cervix has been reported in cases of granulosa-cell tumors and with hyperplasia of the endometrium,[78] but the frequency of this cervical lesion makes the significance of such association very slight. Squamous metaplasia is of course common in cervical polyps (Fig. 6) but here especially trauma and chronic infection appear to be important predisposing factors.

Cancer of the Cervix.—Until very recently it was more or less accepted that cancer of the cervix was due to the chronic irritation subsequent to the injuries of parturition or to chronic cervicitis. A few new facts have recently been brought to light which somewhat shake the dogmatic foundations of the inflammatory theory.

Malignant tumors in mice receiving estrogens have now been produced in some numbers.[20, 21] These tumors are histologically cancer and have the qualities of local infiltration of the tissues of the rectal wall and bladder and of metastasis to the regional lymph nodes. The simultaneous administration of androgens did not prevent the appearance of cancer of the cervix in these animals.

Efforts are also being made to introduce the sex hormones into the background of human cervical cancer. Hofbauer[36] some years ago suggested that the well-known predilection of cancer of the cervix for multiparas was to be explained, not on the basis of the injuries of delivery, but upon the nine months of excessive hormone stimulation to which the cervix is subjected in each pregnancy. In substantiation

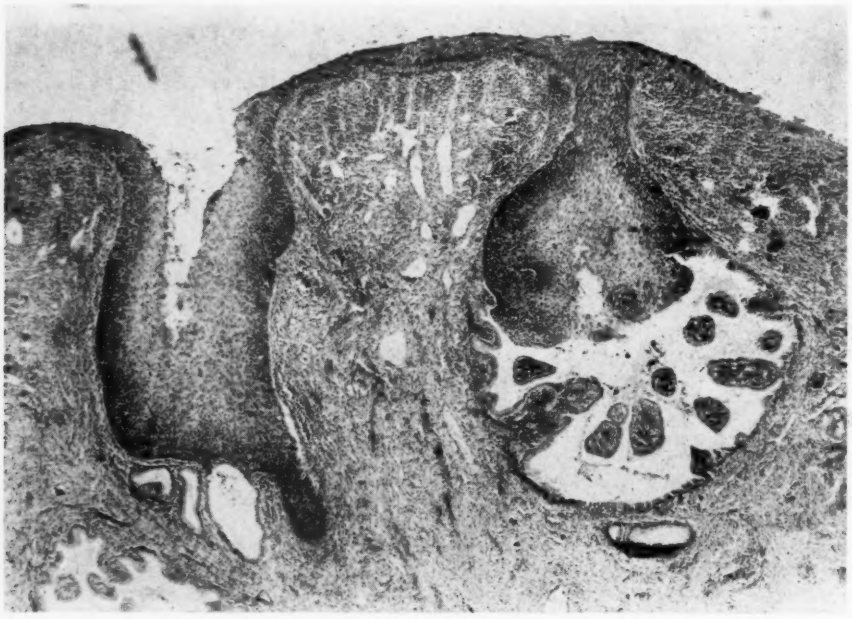

Fig. 7.—Early cancer of the cervix with superficial extension.

of this theory he offered the evidence of hyperplastic changes in the histologic sections from the cervices of pregnant women. These views have received some support from the pathologic studies of Schiller,[68] Hinselmann,[32] and others which have shown that lesions of the cervix regarded as precancerous are not necessarily found in areas of cervicitis or cervical erosion, but on the contrary may appear in the midst of apparently normal epithelium (Fig. 7).

Cancer of the cervix in women does not appear to have any tendency to be associated with other lesions to which an estrogenic causative factor has been theoretically described. Uterine carcinoma associated with breast cancer is apt to be endometrial.[77] Myomas of the uterus seem more often to be associated with corpus than with cervical cancer

in relation to the relative frequency of the two latter conditions.[4, 17, 50, 59] Cervical cancer has not furthermore been reported, to my knowledge, with granulosa-cell tumors, nor has it even been stated that it had any tendency to occur with endometrial hyperplasia.

The excretion of abnormal hormone substances in the urine of patients with cervical cancer has been claimed. Increased excretion of gonadotropic substance was at one time reported, but it has never been clear that this observation was not the result of failure to distinguish the effect of the menopause on gonadotropic substance secretion.[83] Several early workers also reported excessive estrogen excretion, but these observations were based on methods that now must be regarded as quite inadequate. Very recently work has been reported, which still requires confirmation, that women with uterine cancer have abnormal urinary estrone: estriol ratios.[65]

It is interesting, finally, to note that the extensive use of estrogen therapy appears not to have led to any general conviction that the estrogens produce cervical cancer. A report of Gemmell and Jeffcoate[23] in which 3 patients out of 43 treated by estrogens for senile vaginitis and kraurosis vulvae developed cervical cancer is a single report which indicates that caution may be necessary. Geist and Salmon,[22] on the other hand, after treating 206 women for one-half to five and one-half years with total dosages of 500,000 to 23,400,000 international units, noted only regenerative effects and no signs of atypical or excessive proliferation.

CONCLUSION

In attempting to evaluate these diverse observations, a few points become clear. In animals the administration of various hormones, but particularly the estrogens, has been followed by the appearance of neoplasms throughout the reproductive tract. Various species of animals differ greatly in their susceptibility to develop tumors of a certain kind in response to these types of stimuli.

In women tumors morphologically similar to those appearing in animals after estrogen administration develop spontaneously. The benign tumors of this group are pretty sharply limited to the years of ovarian function for their active growth and tend to atrophy after the menopause. In this respect, at least, the ovary is a necessary factor in their development.

Evidence that a specific ovarian dysfunction is the cause is almost complete for certain types of hyperplasia of the endometrium. For the other neoplasias or tumors of the uterus the proof is very incomplete and rests on such indirect evidence as the observed conditions of the ovaries, the association of several tumors in the same patients, and the effects of treatment.

A better understanding of ovarian morphology and of the processes involved in the metabolism of the steroids is required before the hy-

potheses raised by the results of animal experiments can be finally proved for the origin of these reproductive tract tumors in man.

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THE RELATIONSHIP OF HORMONES TO DISEASES OF THE BREAST

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THE relationship of the breast to the ovary has been recognized since the writings of Cooper in 1829.[1] Since then many have emphasized and extended this observation. Recent work has placed this relationship on a more scientific basis and has indicated that other glands of internal secretion may also play a role in the control of the mammary gland. However, it was only since the isolation and purification of the hormones of the hypophysis, gonads, and adrenal glands that changes were produced in the breasts of animals and human subjects which could be ascribed to the action of these secretions. In spite of discrepancies and contradictory evidence, certain facts have emerged which are now generally accepted.

Since it was demonstrated that the hormones were concerned with mammary development and function, it became obvious that they might be of major importance in the genesis of diseases of the gland. That one may better understand the factors which are of possible etiologic significance in the production of benign and malignant breast disease, a knowledge of the histology and physiology of the mammary gland is essential. There are excellent reviews of the endocrine physiology of the breast,[2, 3] so in the following discussion reference will be made only to the more significant studies. It should further be pointed out that much of our present-day knowledge of the breast is based on animal experimentation. Such data are extremely valuable, but caution in their interpretation with regard to the human breast is essential. It is the purpose of this review to present the available information which may bear on the possible significance of the hormones in the production of lesions of the breast.

EVIDENCE FOR AN ENDOCRINE CONTROL OF THE BREAST

The mammary gland must be considered a part of the female reproductive system and as such is subject to the same stimuli throughout life as the other organs of reproduction. Changes in the breast seem to be directly related to those which are seen in the uterus, during the various phases of pituitary and ovarian activity and during pregnancy. The nature of action of the hormones elaborated by the glands of

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internal secretion which have to do with mammary function will be described briefly.

Hormones of the Gonads.—

I. *Ovarian Hormones:*[2, 3]

Estrogens (The Follicular Hormones).—It is now generally accepted that the estrogens are capable of developing the duct systems in the breasts of man and animals. In some species acinar development and occasionally secretion may result from this stimulus only. In animals such as the mouse and rat, ductal change alone is noted, whereas in guinea pigs and the primates such as the monkey, lobule aveolar growth occurs as well. In the human subject, estrogens have produced development of the breasts of both sexes and in individuals of all ages.[4, 5] Evidence from several sources suggests an effect on the periductal connective tissue. The variability in effects may not be due to species differences alone, but may depend also upon the dosage level[6] and the structure of the estrogen used.[7-9] Amounts used above a certain level may fail to show additional physiologic change or hyperplasia[10] or may actually produce stunting of the duct systems.[7, 11]

Progestin (The Corpus Luteum Hormone).—Since estrogens were incapable of developing the breast beyond the duct system in most species, investigators naturally turned to the corpus luteum. In those instances in which no effect was obtained from progestin alone, simultaneous administration of estrogens induced alveolar and lobular growth.[12] There is no question of the effect of progestin in pregnancy.

II. *Testicular Hormones:*

Testosterone and several other androgens are also capable of stimulating the mammary glands in certain species. Ductal development in the rat has been observed by some investigators,[13] while others have noted lobular growth as well.[9, 11, 14] Secretion in the breast of the rat[15] and the monkey[16] has also followed the administration of testosterone and related compounds. Mammary enlargement in eunuchs treated with testosterone is not uncommon.[17] The evidence concerning these actions is not as clear cut as that of the estrogenic effect.

Hormones of the Adrenals.—It is fairly certain that the adrenals are concerned in the genesis and metabolism of the sex hormones. Estrogens and androgens have been isolated from the gland in addition to the known cortical hormones. One of the latter group, desoxycorticosterone has been reported to stimulate mammary growth.[9] The adrenals may also be concerned in lactation, but it is possible that this is more closely related to the effects of carbohydrate, water, and salt metabolism rather than to a specific action.

Hormones of the Pituitary Gland.—In recent years evidence has accumulated that the hypophysis is also necessary for mammary growth. Two types of hormones have been described.

I. *Mammogenic Hormones:*[3, 18]

Mammary involution occurs rather promptly after hypophysectomy. It has been reported that the changes usually produced in the breast of animals by estrogens and androgens are not found when the hypophysis is previously removed. Although there have been reports to the contrary, these findings suggested the possibility of a hormone elaborated by the hypophysis. Evidence suggests the existence of such a mammogenic hormone. Turner and his associates postulate that two such hormones may exist. One they term Mammogen I, which they believe responsible for ductal development, and the other Mammogen II, which may cause lobule-alveolar growth.[19] They further believe the former hormone is stimulated by estrogens and androgens and the latter by progesterone and estrogens. Whether these hormones act directly upon the breast or are necessary for the action of the other hormones is not settled.

II. *Lactogenic Hormone:*[3, 18]

The production of lactation under certain conditions by anterior pituitary extracts led to investigations which resulted in the isolation of a specific lactogenic hormone from the hypophysis—prolactin.[20, 21] Lactation could not be induced in an undeveloped breast, but it was demonstrated subsequently that suitable stimulation by the ovarian hormones was also necessary. Prolactin has recently been highly purified and it has been suggested that this hormone, rather than the mammogens, may be a more important factor in mammary development.[22]

These facts emphasize the pituitary-gonadal relationship. They indicate that normally a balance exists between the hormones of these glands; an alteration in this balance may give rise to atypical changes in the organs upon which the hormones act.

EVIDENCE FOR A NERVOUS CONTROL OF THE BREAST

Evidence exists that the nervous system is involved in some fashion in the physiologic responses of the breast. Suckling in the virgin rat has resulted in mammary development, lactation, and inhibition of the estrous cycle.[23] This presumably works reflexly by way of the hypophysis. In women suckling certainly plays an important role in the maintenance of lactation. Moreover, there are numerous instances cited of lactation and breast changes in children, the virgin female, and even in the male after stimulation of the nipple alone.[24] Many lesions of the breast are associated with disease in the pelvis, which may affect the breast not only by disturbances of ovarian function, but by way of the pelvic sympathetic nerves.[25] It must be inferred, therefore, that the nervous system is important in the maintenance of mammary function, but probably in an indirect manner, since the elaboration of hormones may be partially initiated by or dependent upon nervous stimuli.

HISTOLOGIC CHANGES IN THE BREAST DURING THE MENSTRUAL CYCLE

There is evidence that a cyclic change occurs in the breast, which can be correlated with a rise and fall in ovarian activity during the menstrual cycle. One group of writers maintains that in the latter part of the menstrual cycle there is sprouting of the ducts to form acini, which almost completely disappears in the postmenstruum.[26, 27] Others, however, believe this cycle of epithelial proliferation and regression to be exaggerated and are of the opinion that the most striking feature is edema of the connective tissue during the premenstruum.[25, 28] There is also vacuolization of the cells which suggests a secretory phenomenon. Studies of whole sections of the breast have shown that the degree of activity is not similar throughout.[24] This has been attributed to the lack of uniform response to a given stimulus. A similar reaction is known to occur in the endometrium. Since most of the studies were made on small areas of breast tissue, it is apparent that no concrete conception of the changes can be fully determined until whole sections are made from many normal breasts throughout the cycle.

Conclusions.—Complete development of the breast is manifested by the presence of certain static structures (ducts, lobules, and acini). Variations of these structures may occur during the menstrual cycle as a result of rhythmical stimulation with the hormones. We have concluded that the breast is prepared each month for pregnancy, since it is subject to the same influence as the uterus. Like the uterus, it has both its proliferative phase induced by estrogens and its secretory phase by progestin and the anterior pituitary. A process analogous to menstruation then occurs which is represented by some involutional change and absorption of the secretion if pregnancy does not ensue. It is only by accepting these possibilities that one may have a concise and logical explanation for the hormonal and nervous action on the breast, with the resultant changes during catamenia, pregnancy, lactation, and the disease states to be described.

PHYSIOLOGIC CHANGES IN THE BREAST AT VARIOUS PERIODS OF LIFE

Birth.—Activity of the mammary ducts in newborn infants is common. Witches milk also occurs in a fairly high percentage of these babies. This activity probably originates from the hormones of the pregnant mother, since practically complete regression of the infant's breast tissue follows shortly after delivery.

Puberty.—After birth the breasts are inactive until the changes leading to puberty appear. In the female, development of the breast usually appears about the tenth year and this is associated with a definite increase in activity of the gonads.[29] At first the changes are confined to the ducts and periductal connective tissue, but even before the menarche there is evidence of acinar and lobule formation. In the

male between the ages of 12 and 17 years there is also a change in the breast.[30] The histologic picture is similar to that observed at the onset of breast growth in the female. These changes usually subside spontaneously in contrast to those in the female, where there is usually continued mammary development once the cyclic activity of the menses is established.

Adult Cyclic Female.—In the normal adult female there appears to be a cyclic change in the breast associated with the fluctuations of hormonal secretion during the catamenia. Whether these changes are purely epithelial, vascular, secretory, or combinations of these is a matter of dispute. At any rate there seems to be no doubt that mammary changes do occur during the menstrual cycle and that as stated before they are dependent upon ovarian and pituitary secretions.

Pregnancy and Lactation.—The changes which occur during pregnancy and lactation are well recognized and are certainly controlled to a large extent by hormonal secretion. The changes in the breast in the first half of pregnancy are rapid growth of the lobules and epithelial proliferation. In the latter half the acinar epithelium enlarges and secretes, thus causing distention of the acini.[3] During pregnancy the placenta is probably the main source of stimulation, whereas during lactation the pituitary gland is most likely the dominant activator of mammary function.

Climateric.—At the menopause when the ovarian stimuli recede to a low ebb, the mammary glands exhibit regressive changes. In some instances, evidence of activity in the breast is apparent years after the cessation of the menses. This may be caused by a continued but lowered secretion of an activating hormone, possibly from the ovary. In other cases, particularly late in life, there may be an almost complete atrophy of the gland.

In summary it may be stated that mammary development, growth, and regressive changes are dependent upon the rise and fall of hormonal stimuli principally from the gonads and the hypophysis. The exact mechanism by which the metamorphosis takes place is still obscure, but present knowledge allows at least a working hypothesis for the understanding of some of the diseases of the breast to be described.

PRECOCIOUS DEVELOPMENT (INFANTILE HYPERTROPHY)

Aside from the changes noted at birth there are numerous instances of premature mammary development in children. These are usually associated with demonstrable lesions, although in some cases the etiology is vague.

Specific Associated Factors.—

Lesions of the Third Ventricle: Tumors, defects, and inflammatory lesions in the region of the third ventricle give rise to true pubertas praecox. The breast changes are merely part of the general picture

of developmental and sexual advance. The most probable explanation for the effect is a stimulation of the hypophysis via the hypothalamus and infundibulum. Ovaries of these patients show marked follicle stimulation and cyst formation and in one instance a true corpus luteum has been reported.[31] The breasts exhibit ductal development but rarely lobule formation. This activity in the ovary probably initiates the secretion of the hormones, which in turn causes growth of the secondary sex organs including the breast. This thesis is confirmed by assays of the urine of these patients, which usually show increased levels of gonadotropic hormone, estrogens, and 17-ketosteroids (androgens).[32]

Lesions of the Adrenal Cortex: In general, neoplasms of the adrenal cortex in the female child produce masculinization, but there are cases in which the first signs are feminization.[33] Since the adrenal gland is a probable source of estrogens it is possible to explain the early mammary hypertrophy on this basis especially since excretion studies reveal increased amounts of the hormone.[31] When masculinization and regression of the breasts occur, they are accompanied by significant increases in the androgenic output even though the estrogen levels usually remain elevated. Thus, it is reasonable to assume that this reversal is of androgenic origin and therefore that the androgens are not responsible for the original breast hypertrophy.

Ovarian Lesions: Among the associated exciting factors of premature mammary development are lesions such as the granulosa-cell tumor and teratoma of the ovary. These lesions when active are usually associated with generalized feminization, accompanied breast enlargement, uterine bleeding, and cornification of the vaginal epithelium. This syndrome must be distinguished from true pubertas praecox. However, here as in the other states, the breast changes are probably due to estrogens elaborated by the lesions, since the cells involved are those which presumably produce the hormone. Assays of the urine in most instances reveal elevated excretion levels of estrogens, whereas the titres of the other hormones remain normal.[31]

Idiopathic Breast Development.—In a few children premature breast development occurs without known cause. Other secondary sex changes are usually normal or only slightly advanced. Histologic examination reveals ductal development, but for the most part assays of the urine for hormones do not reveal any abnormalities.

Hormonal Induced Infantile Hypertrophy.—It has been the experience of many that administration of estrogenic hormone to the female child for gonorrheal vaginitis frequently results in mammary growth. There is no question that these changes are due to the hormone since regression occurs rather rapidly after cessation of treatment.

Conclusions.—The available evidence suggests that premature mammary development is due in large part to the effect of the estrogenic hormone. It is probable, particularly in lesions of the third ven-

tricle, that the pituitary hormones are also a factor. Histologically the changes are confined for the most part to the duct system and periductal connective tissue. Thus, they correspond to the state produced by a known stimulus and in this sense represent a physiologic response to premature or excess secretion of the hormones. Removal of such a stimulus is followed by a rapid regression to the normal state.

HYPERTROPHY OF THE BREAST

Asymmetrical Prepubertal Hypertrophy.—At about the age of 10, when normal breast development usually commences, there may be a rapid growth of one breast which is out of proportion to that of the other breast. This is commonly referred to as early ripening and is not true hypertrophy. Eventually the more slowly developing breast usually attains the size of the larger breast and at the time of puberty both are of almost equal size and within normal limits. Since in most females the breasts are not identical in size, this seems to represent an exaggeration of a normal phenomenon. Histologically the changes are no different than those in the normal adolescent. Estrogen excretion is usually normal. The early inequality is explained by some investigators as an increased sensitivity of the involved organ to a normal physiologic stimulus.[34]

Pubertal and Postpubertal Hypertrophy.—Pubertal and postpubertal hypertrophy abnormalities may be classed as true hypertrophy. The process is either unilateral or bilateral and is easily distinguished from early ripening by the size of the breast. It may manifest itself at puberty although similar changes are associated with pregnancy and lactation. Histologically there is an increase in ductal growth, but connective tissue increase is more striking. Lobular development is rare especially in the virginal type. Estrogen assays are usually normal, but may show elevated levels of the hormone. Again, as in early ripening, the changes may be due to an excessive stimulation or to increased sensitivity of the breast.

FIBROADENOMA OF THE BREAST

Observations suggest that these tumors may be of hormonal origin. It is possible that they may arise as a result of abnormal or excessive stimulation, since they usually occur when the metabolism and secretion of the sex hormones are at their height and may, in addition, be abnormal.

Clinical Aspects.—The lesions seldom develop before puberty or after the menopause, except possibly in the presence of a granulosa-cell tumor or similar abnormality of the ovary. They are seen most frequently in the second and third decade. It has been suggested that fibroadenomas occur most frequently in women of a definite constitutional type, that is, nulliparous females with a relative underdevelopment of the pelvic organs and breasts.[35] The menstrual cycles of

patients with fibroadenomas of the breast are seldom abnormal, but some give a history of a period of atypical cycles following the menarche. Endometrial biopsies on such patients do not reveal any gross abnormality. Since these lesions arise most frequently prior to pregnancy, the reproductive history is not of significance. The incidence of pelvic disease in patients with fibroadenoma is relatively small when compared with that in other types of benign breast disease. Abnormalities present in the earlier years are usually underdevelopment of the pelvic organs or are congenital in origin.

Experimental Studies.—Studies on the occurrence, alteration, and production of these lesions in the experimental animal and the human being are of interest with regard to the possibilities of hormones as etiologic agents. It has been reported that estrogen pellets or estrogens with prolonged activity produce a high percentage of true fibroadenomas in a strain of rats which ordinarily have a low spontaneous incidence of the disease.[36] Although others have been unable to confirm these findings, neither the method of estrogen administration nor the strain of rats was identical.[37] In our clinics, patients have been given estrogens over a long period in the presence of and following the removal of fibroadenomas. No new tumors have been observed which could be attributed to the hormone. On the other hand, it is not uncommon for new lesions to arise spontaneously when others are already present. Regarding the activity of fibroadenomas under hormonal influences, there can be little doubt. Changes have been observed in the size and histology of the tumors during the menstrual cycle,[27] pregnancy, and lactation.[38, 39] Androgens decrease the glandular elements in both the spontaneous and transplanted fibroadenomas of rats and may convert them to fibromas.[40, 41] Studies in this laboratory reveal that androgens may produce atrophic changes in the breast epithelium and may actually cause disappearance of the terminal tubules of the mammary gland of the mouse. In short, therefore, fibroadenomas, at least in the experimental animal, unlike carcinomas of the breast are subject to the same changes as normal breast tissue. It is difficult to see why a circulating hormone should not affect the breast uniformly. Yet there is evidence that the response of the breast is not uniform to such a stimulus. Since the histologic characteristics of the fibroadenoma are similar to those seen in the normal breast, it has therefore been suggested that the lesions are not actual tumors but because of a localized sensitivity represent a specific response to normal stimuli.[6, 34]

Excretion Studies.—Studies of the urinary excretion of estrogens have been carried out in eight patients with the disease.[42] Some of the patients developed more tumors during the period of observation. Assays were continued throughout a minimum of one menstrual cycle. In the majority of cases the monthly curve of excretion resembled those

of normal controls in the same age group although a few had atypical curves. The latter may represent an abnormal excretion, but there is no direct evidence that they are characteristic for the disease. The process is slow and since all patients were studied after the onset of the disease it is possible that abnormalities may have been present earlier. The findings do not prove that estrogens are not involved since, as stated before, the tumors may arise as a result of a localized response to normal stimuli. Furthermore, excretion rates as will be pointed out later, must be interpreted with caution, since they represent only one index of activity.

Conclusions.—There is a suggestion that estrogens are involved in the initiation of fibroadenoma of the breast. The lesions are usually slow growing and, although not noticed, may arise in the early years after the menarche when atypical menstrual activity is not uncommon. They resemble the changes seen in early ripening and hypertrophy and may represent a more localized response to a normal stimulus. There is no direct proof, however, that the hormones are the exciting agents, in spite of histologic alteration during various physiologic states or after hormonal administration. The possibility of a definite constitutional type must be considered. One is forced to conclude, therefore, that factors other than hormones may be operating as well.

CHRONIC MASTITIS, CYSTIC DISEASE, AND PAPILLOMAS

The terms chronic mastitis or chronic cystic mastitis have been used to denote a variety of benign lesions without obvious tumor formation. It is now recognized that some of the lesions included under such diagnoses can be distinguished as definite entities. For an understanding of possible causative factors it seems preferable to establish a working classification, based on clinical and microscopic observations. No one classification has been found to be satisfactory because of disagreement among pathologists and clinicians. The classification to be offered here is not original, but is an attempt to combine our own observations with those of others. Even though there are obvious discrepancies, it is helpful in differentiating the various manifestations of breast disease and their possible causative factors.

Adenofibrosis.—A syndrome for which Taylor[43] has suggested the term adenofibrosis seems to be a distinct entity. Semb[44] has referred to the lesion as fibroadenomatosis. Probably the earliest signs and symptoms are those of premenstrual swelling and pain associated with tenderness of the breast. The relief usually following the onset of the menses is dramatic. This early stage is commonly referred to as mastodynia or mastalgia. The physical signs are usually minimal and, beside slight premenstrual swelling and venous engorgement, may show only a slight thickening in the upper outer quadrant. Histologically there may be only a slight increase in the periacinar connective

tissue, and edema. As the process continues, the symptoms and signs become more prominent. There may be only an accentuation of nodularity in the upper outer quadrant, but usually the process is more diffuse. There is an increase in density of the entire gland, which is well differentiated from the overlying skin, the subcutaneous tissue, and the underlying structures. In the advanced cases, the entire breast resembles a saucer or disc and a definite edge can be palpated. The gland may be finely granular or moderately nodular, and in the premenstruum exhibits marked swelling and venous dilatation. Histologically there is usually a marked increase in the connective tissue stroma with loss of or defective lobule formation. Frequently in addition to the stromal change there is proliferation of the acini, although the epithelium itself may not show activity. Many variations of the process may be seen. In most cases venous engorgement and edema are prominent features, especially in the premenstruum. This may account for the typical cyclic pain. It appears to be the basic process and other features such as epithelial proliferation may be superimposed as a later manifestation.[45] For a detailed and excellent description of the syndrome and its histologic features one is referred to the work of Taylor and Waltman.[45]

Clinical Aspects: Adenofibrosis most commonly occurs in the second and third decade of life, and in this respect resembles the fibroadenoma. Regression occurs after the menopause or following castration. A study of the menstrual cycle by most observers reveals that shortened intervals accompanied by a scant flow of short duration is not uncommon.[34, 35] The cyclic character of the pain during the cycle has been described. Endometrial biopsies usually reveal normal patterns. The incidence of sterility is relatively high. In those women who have borne children, the process is sometimes seen after a long period of infertility. Disease of the pelvic organs frequently accompanies the breast change. Taylor is of the opinion that so-called pelvic congestion or chronic parametritis is a salient associated lesion.[25] Permanent changes may thus result from such chronic congestion. He further believes that these two conditions may be produced by a similar process, which is at least partially dependent upon disturbances of the vascular and nervous systems. Such disturbances may possibly arise from, or may lead to, endocrine dysfunction.

Experimental Studies: Many attempts have been made to reproduce these lesions in experimental animals. Geschickter[46] injected rats with a daily maximal physiologic dose of estrone and noted changes resembling adenofibrosis. This was also obtained by combining injections of progesterone or testosterone with larger doses of estrone. Taylor and Waltman[45] were unable to produce these lesions in mice. These differences may possibly be reconciled by a consideration of the type and dosage of hormone used and by difference in the strain or

species of experimental animal. The production of edema may be due to the hormones of the ovary since they have been shown to cause retention of fluid.[47] Increased vascularity may be produced by estrogens, although nervous stimuli may be responsible either by a direct action or indirectly through activation of hormonal secretion.

Excretion Studies: Taylor[25, 43] could find no gross abnormality either in the total output or the configuration of the monthly curve of estrogen excretion. Bucher and Geschickter[48] made similar observations but stressed the total output. Nathanson[49] studied the cycles of excretion but did not attempt to estimate the total output since the configuration of the curve was considered more significant. Some of the patients exhibited atypical curves although such abnormalities were not constant from month to month. An analysis of several of the curves presented by Taylor and Bucher and Geschickter also suggests a similar anomaly of excretion, which is not usually found in a woman with a normal cycle. When one considers the configuration of the excretion curves, these three studies seem to be in essential agreement with regard to estrogen excretion.

A study of the possible role of the corpus luteum hormone has also been made. Nathanson noted a lowered excretion of pregnandiol in only a few of the cases studied while Bucher and Geschickter found similar changes in all of their patients. Assays of the gonadotropic hormone by Taylor and by Nathanson revealed no gross alterations.

Conclusions: Adenofibrosis of the breast represents a distinct entity. The secretions of the ovary seem to be a prerequisite for the production of the syndromes although they may not be the exciting factors. Nervous stimuli, vascular reactions, and the mechanism of hormonal secretion are closely interwoven, so that all three factors may be involved in the process, particularly regarding the edema and congestion. Excretion studies are slightly suggestive of a hormonal imbalance. The possible role of unopposed or atypical stimulation by the hormones also remains to be clarified. Slight abnormalities of the menstrual cycle and associated pelvic disease suggest a hormonal etiology. It can be concluded as in the case of fibroadenoma that the hormones are possibly involved but that other factors are also necessary for the production of the syndrome.

Nonpuerperal Secretion.—The salient feature of this type of breast disease is discharge from the nipple which may be accentuated before the menses. The process is sometimes associated with swelling and cyclic or acyclic pain. The discharge may abate at the menses, but usually persists throughout the cycle. It may be serous or resemble colostrum and show varying degrees of viscosity. It is to be distinguished from the serosanguineous or sanguineous discharge so frequently associated with duct papillomas, marked epithelial hyperplasias, and carcinoma. Examination usually reveals dilatation of the

ducts, especially near the areola, and slight nodularity elsewhere in the breast. The nipples are frequently crusted and the mammary tissue itself is ill-defined. If secretion is not obvious, removal of the crust with gentle pressure on the breast usually results in the escape of fluid from the nipple. On gross and microscopic examination the ducts are dilated and contain secretion, desquamated cells, and debris. Frequently, cheesy inspissated material is seen. Hyperplasia of the duct and acinar epithelium may be superimposed.

Clinical Aspects: These lesions occur most frequently during the third and fourth decades. Many cases appear at onset of the menopause. Remission of symptoms and signs is of frequent occurrence after castration or when the menopause is complete. The menstrual cycles may be normal, but prolongation of the interval is common. In contrast to the findings in adenofibrosis the endometrium is frequently atypical. Absence of the secretory phase is most common, although hyperplasia is relatively rare.[50] In contrast to adenofibrosis, many women with this disease have borne children. Lactation may be normal but faulty lactation or premature weaning frequently precedes the onset of the disease. Pelvic disease is fairly common in this group. Ovarian cysts predominate over other abnormalities.

Experimental Studies: Prolonged injection of estrogens in mice results in changes similar to those described in the human being.[45] The rat also shows a similar reaction particularly when estrogen administration is followed by prolactin.[6, 11]

Excretion Studies: The excretion of estrogens throughout the menstrual cycle is definitely atypical in a high percentage of cases. It was found that the peaks ordinarily seen at the time of ovulation and at the height of corpus luteum function were frequently absent.[51] Moreover, the daily excretion was somewhat lower than that observed in normal subjects. Taylor[43] also came to the same conclusion from an interpretation of the configuration of the curve and the total monthly output. Pregnandiol excretion in these patients is usually lower than normal.[51] There is no consistent abnormality in the excretion of the gonadotropic hormone, although there is a suggestion of an excessive output particularly in the premenopausal group.

Conclusions: Nonpuerperal mammary secretion seems to be due to endocrine dysfunction. It is akin to lactation and is frequently allied with abnormalities of the process. It is probably due to an ovarian dysfunction, in which the normal cyclic secretion of estrogens is absent. Deficiency of the corpus luteum as evidenced by lowered pregnandiol excretion and atypical endometrial biopsies is also of importance. Such a state is suggestive of an anovular cycle, a state which often occurs in the premenopausal period when the breast lesions frequently make their appearance. The process could, therefore, be caused by continuous estrogen stimulation, which is unopposed or not supple-

mented by the corpus luteum hormone and, thus, may be analogous to the production of similar lesions in mice. As a part of the dysfunction there may be an alteration of the pituitary secretion, so that this, too, may be a factor in the production of the syndromes.

Combined and Miscellaneous Types.—Unfortunately, many of the lesions seen by the clinician are not as clear cut as those described. There may be combinations of adenofibrosis and nonpuerperal secretion. Others may show, in addition, cyst and papilloma formation. The latter may be superimposed on the two basic lesions described.[45] Such a phenomenon may occur when the less complicated lesions are of long standing and are subjected to continuous or new stimulation. This group of mixed lesions leads to the greatest confusion in diagnosis and interpretation of causative factors. At present because of an incomplete understanding of these types, it is difficult to evaluate possible exciting factors. Lesions resembling the various types have been produced in animals by various hormones, particularly the estrogens. At any rate one may be safe in assuming that factors concerned in the production of the more clear-cut lesions may also be responsible in the production of this heterogenous group.

Cystic Disease of the Breast.—

Clinical Aspects: True cystic disease of the breast may manifest itself in a variety of forms. It usually occurs in women in the latter part of active sexual life and is especially common about the time of the menopause. Unlike adenofibrosis or nonpuerperal secretion, regressions following the menopause are infrequent. Diseases of the breast such as those described may precede cystic disease. The menstrual cycles are usually normal. Cyclic swelling and subjective and objective symptoms other than the presence of lumpiness of the breast are conspicuously absent. The disease occurs most frequently in the childless woman, and the incidence of coexistent pelvic disease is not unusual. The physical findings are well recognized, but the process must be carefully distinguished from the lesions previously described.

Three well-defined types are seen:

1. Cysts without epithelial hyperplasia
2. Multiple cysts with epithelial hyperplasia (Reclus' disease)
3. Multiple cysts with marked epithelial hyperplasia and papillomatous change (Schimmelbusch's disease, adenosis).

The solitary cyst is primarily of duct origin, while the lesions with multiple cysts may show the greatest change in the acini.

Experimental Studies: The various manifestations of cystic disease in the woman can be duplicated by the administration of estrogens alone[52, 53] or in combination with prolactin[6, 11] to the experimental animal. Some believe estrogens to be the causative agent in the human being and Geschickter has reported the development of cystic disease following

such stimulation in the woman.[34] In our experience even when the hormone is given to patients with the disease, no changes have appeared which could be ascribed to hormonal administration.

Excretion Studies: In this laboratory, no constant pattern of excretion of estrogens was found in patients with cystic disease. As in the other types of benign breast disease, atypical cycles of excretion were encountered, but the deviation from normal was not sufficiently great to warrant an assumption that they were significant. Pregnandiol excretion was also variable. Bucher and Geschickter[48] found extremely low values of pregnandiol in two cases and equivocal curves of estrogen excretion.

Conclusions: Cystic disease in the human being can be simulated by the administration of hormones to animals. Other evidence, also, suggests the internal secretions as participating agents. However, as in most other processes ordinarily included under this heading, the data are still far from conclusive regarding the hormones as the primary cause.

BENIGN BREAST DISEASE IN THE MALE

As in the female, benign disease in the male breast is erroneously designated as mastitis. Some refer to most types as gynecomastia, but this should be reserved for a special group.

Adolescent or Puberty Mastitis.—In the male, this is akin to that seen normally at the onset of the breast development in the female. It usually appears between the twelfth and seventeenth years. It is characterized by the presence of a well-defined, freely movable, discoid mass beneath and closely associated with the areola. The mass may vary in size from less than 1 to 5 cm., but as a rule is 2 to 3 cm. The nipple and areola may also be increased in size. The process is usually unilateral at the onset, but may affect both breasts, simultaneously or successively. It occurs more commonly than is generally recognized. Jung and Shafton in approximately 1,000 examinations found that it was an integral part of the process of puberty.[30] It is not seen more often because of the frequently transient character of the process, which may arise and regress within even a month. Histologic examination reveals lengthening and hypertrophy of the ducts, with an increase in periductal connective tissue. Lobule formation is usually absent. In a small percentage of cases this lesion persists and may then be correctly called gynecomastia.

Gynecomastia.—In the abnormality of gynecomastia, the contour and elements of the breast approach that of the normal woman. As stated previously, it may represent a persistence of the adolescent type or may arise spontaneously in the adult in the presence of associated diseases. It may be unilateral or bilateral. Histologically, in addition to the changes described, there may be hyperplasia of the duct epithelium, dilatation of the ducts, and occasional secretion. The presence of acini

and lobules is rare. The main differences from the other types of benign breast disease in the male are the persistence and the physical characteristics.

Senescent Mastitis.—After the age of 45 years, but particularly after 60, changes resembling those seen at puberty are frequently encountered. Some, of course, may occur earlier. The disease behaves in a fashion similar to that seen in the youth, but spontaneous regression is not as common.

Possible Etiologic Factors.—In the large majority of cases, there are no obvious associated abnormalities. Adolescent and senescent mastitis, as noted, occur at the extremes of active sexual life. It is possible, therefore, that at these periods there is a temporary hormonal imbalance. However, both mastitis and gynecomastia may occur in association with other diseases and in these instances possible etiologic factors are apparent. These may be described as follows:

1. Atrophy of the Testicle Following Orchitis or Injury. The spermatic tubules are most commonly atrophied and the atrophy thus accompanied by a relative or actual increase in the interstitial cells. Since the latter are supposedly the site of origin of androgens, it is possible that they are responsible for the change in the breast.

2. Neoplasms of the Testes. Gynecomastia is sometimes associated with tumors of the testes, particularly the chorioepithelioma. Gilbert[54] is of the opinion that the breast lesions are of two types: (1) a "physiologic" type resembling the usual mastitis in males and not necessarily related directly to the tumor of the testes; (2) a "choriogenic" type most frequently related to the chorioepithelioma, and resembling the female breast in its histologic characteristics, especially during pregnancy. The pituitary gland in cases with "choriogenic" gynecomastia shows changes which are also seen in pregnancy. In contrast to the physiologic type, these lesions may be caused by the hormones secreted by the tumor itself. Several cases of gynecomastia have also been associated with interstitial cell tumors of the testes. The nature of the stimulus is not clear, for although one would expect the androgens to be in excess, one patient[55] had loss of libido suggesting destruction of testicular function and failure of the tumor to secrete a hormone to maintain such a function.

3. Functioning Tumors of the Adrenal Cortex in the Adult Male. These may produce feminization in contrast to the usual masculinizing syndrome seen in females and young males.[56, 57] The syndrome is characterized by mammary enlargement, regression of secondary sex characters, and atrophy of the testes. Since estrogens as well as androgens have been recovered from the adrenal gland, and because elevated excretion levels of both of these substances are frequently found in patients with adrenal cortical tumors, a hormonal cause seems evi-

dent, especially since removal of the tumor is followed by regression of the breast lesion.

4. Hypophyseal Adenoma.[58] These lesions may give rise to atypical pituitary secretion which may affect the breast directly or indirectly as a result of stimulation of the peripheral endocrine organs.

5. Cirrhosis of the Liver. Breast changes associated with cirrhosis are sometimes encountered.[59] The patients commonly show associated testicular atrophy. It is conceivable that the breast lesions may be caused by faulty metabolism of the hormones as a result of the cirrhosis, since the liver is intimately concerned with such a metabolism. An alternative possibility is a loss of testicular function.

6. A Syndrome Characterized by Aspermatogenesis, Testicular Atrophy, and Gynecomastia Without Known Cause, as reported by Klinefelter and co-workers.[60] The testicular changes resembled those seen after orchitis or injury, and may possibly fall into the same category.

7. Other Conditions. The mechanism involved in the production of mastitis in patients having thyrotoxicosis,[61] leucemia, and other diseases is not clear. It seems, however, that in these diseases there is also a disturbance in the metabolism of the hormones.

8. Hormonal Induction of Mastitis and Gynecomastia. Mastitis of a transient character develops in eunuchs following the injection of testosterone.[17, 62] Such treatment is followed by an increased excretion of estrogens in the urine and suggests, therefore, a metabolism or conversion of the androgens to estrogenic substances.[63-65] This may be characteristic for the eunuch, since such changes after administration to a normal individual are exceedingly rare. As would be expected, the administration of estrogens to the male results in mammary hypertrophy.[66-69] The nipples and areola enlarge and in some cases there is marked epithelial proliferation and acinar formation. Removal of the stimulus allows for relatively rapid regression of the process.

Excretion Studies.—

Adolescent Mastitis: A study of the excretion rates of the sex hormones in adolescent mastitis has revealed that in many instances the process is associated with atypical urinary excretion rates of estrogens and 17-ketosteroids, probably as a result of sexual metamorphosis.[70] From the data, it appeared that the mastitis occurred in the presence of a hormonal imbalance in which the estrogens played the more important part. The syndrome was more closely related to the ratio of the estrogens to the 17-ketosteroids than to individual rates. There was evidence of pituitary hyperactivity in some cases, but the data were not conclusive.

Senescent Mastitis: Changes in sex hormone excretion similar to those of the adolescent type are usually found.[71] The estrogens are within normal range, the 17-ketosteroids below normal, and the gonadotropic

titer almost always elevated. It should be pointed out that these levels are similar to those observed in the older male, particularly at the climacteric, so that their significance is open to question.

Gynecomastia and Mastitis in Association With Known Abnormalities: Gynecomastia without known cause is accompanied by excretion rates of the hormones much like those of the adolescent and senescent types. Frequently the values are normal, but it should be remembered that the studies in most cases were made after the process became static. When there are associated abnormalities, hormonal excretion is usually atypical. Certain testicular neoplasms, especially the embryonal carcinoma and the chorioepithelioma, give rise to marked elevations of anterior pituitary-like hormone which, as far as can be determined, is similar to that excreted in pregnancy.[72] Moreover, significant elevations of estrogen excretion may be found in patients with associated gynecomastia and chorioepithelioma.[54] Androgen excretion is variable depending upon the extent of testicular destruction. In one case of interstitial cell tumor an increase of the gonadotropin titer was found.[55] Cases of feminization due to adrenal cortical carcinoma show estrogen levels out of proportion to the androgen excretion rates.[57] The hormonal excretion in patients with hypophyseal adenoma has not been studied, but there is reason to suspect that atypical excretion levels are present. Klinefelter and his associates[60] found increased follicle-stimulating hormone (gonadotropic hormone), normal to lowered 17-ketosteroids, and normal estrogens in their patients with aspermatogenesis. They are of the opinion that the breast lesions are not due to hyperestrinism nor androgens alone, but rather to a combination of androgens and lack of inhibin (a hormone similar to estrogens secreted by the testicular tubules). Glass and associates[59] studied the excretion of estrogens and androgens in males with mastitis and hepatic disease. They found low androgen values and elevated levels of the free estrogens. The testicular atrophy associated with these cases may account for the low androgen levels, and faulty metabolism in the liver might explain the high values of estrogens.

Conclusion: Benign breast disease in the male seems to be associated with an endocrine imbalance, either as a result of sexual metamorphosis or of an associated abnormality or tumor. Since the changes normally produced by the various hormones are not identical, clarification may come when a careful correlation is made between the histologic appearance of the breast and a known activating agent. A common denominator may be found in the mammogenic hormones. As stated previously they may be activated either by estrogens or androgens. Hence, similar lesions could be produced by these different hormones. Most of the available data point to the estrogens as an important factor. Changes induced in the breast by the administration of estrogens are seen frequently, but except in the eunuch testosterone seldom produces obvious breast abnormalities. Moreover, testosterone has been

used with success in the treatment of the more transient types of mastitis. These paradoxical findings may possibly be explained by a difference in the metabolism of the hormones as a result of disease or alteration of the endocrine status of the individual.

CARCINOMA OF THE BREAST

Numerous observations have been made suggesting a possible relationship between the glands of internal secretion and carcinoma of the breast. These studies, both clinical and experimental, are of importance since they have provided tools and leads by which one may search for a specific cause of the disease.

Experimental Studies.[73, 74]—The work of Tyzzer,[75] Slye,[76] and others established the importance of heredity in the development of tumors in mice, but later work suggested that other factors were also involved.[77] Lathrop and Loeb, in 1916, demonstrated that castration caused a marked reduction in the incidence of spontaneous mammary carcinoma in mice with a high susceptibility to the disease. It was later shown that the reduction in rate varied directly with the age of castration, that is, the earlier the ovariectomy, the lower the incidence. Castration also delayed the appearance of tumors when they did arise.[79, 80] However, when female mice of a normally high-tumor strain were spayed immediately after birth the incidence of breast tumors was higher than in mice castrated at maturity.[81] It was suggested that the adrenal glands substituted for the ovaries, since mammary and uterine stimulation was noted and adrenal cortical hyperplasia developed later in life. Murray[82, 83] found that mammary cancer could also be produced in males of highly susceptible strains by the transplantation of ovaries of their sisters, and also noted a lower rate in virgin females. Bagg[84] observed that forced breeding increased the incidence of mammary tumors. Fekete found that the mammary glands of mice of high-tumor strains showed more proliferation during pregnancy in contrast to those of a low-tumor strain during the same period. Moreover, regression of the glands in the high-tumor strain was incomplete after parturition.[85] These experiments suggested the importance of the ovary in the production of the lesions. Attempts to produce breast cancer in the animal by the use of estrogenic substance were not successful until the work of Lacassagne in 1932.[86] By the administration of the hormone, he was able to produce cancer in male mice which never have the disease, although the incidence in the females of the same strain is high. It was not possible, however, to initiate cancer in males belonging to a very low mammary tumor strain.[87] Many others have since confirmed and extended the work.[73, 74] They have reaffirmed the influence of heredity as a necessary factor in oncogenesis, regardless of the other agents involved. Recently, it was shown by Bittner that another factor which was present in the milk of high-tumor strains was also essential.[88, 89]

By suckling newborn females of a low-tumor strain on mothers of a highly susceptible strain, the incidence of tumors could be significantly increased. A reduction in rate was seen when the reverse procedure was carried out. Twombly[90] utilized this technique and was then able to produce breast cancer in the males of low-tumor strains by the administration of estrogens. Thus, it has been demonstrated that factors other than the estrogens alone are necessary for the production of mammary cancer. It has been maintained that the extent of response of breast tissue of nonsusceptible animals to estrogens is limited regardless of the duration of administration or the amount of hormone given. Factors which ordinarily control cell growth may act to prevent further progression of the cells to a malignant state. Defects in the governing mechanism may allow for neoplastic changes, providing the cells are susceptible. The recent report of Geschickter[36] is at variance with this point of view. He has reported a high incidence of mammary cancer induced by prolonged administration of estrogens in rats of a nonsusceptible Wistar strain. Metastases were also described. Noble and collaborators[91] using essentially the same technique in a different strain of rats noted tumors which were extremely hyperplastic, but there was no evidence of invasion of the stroma or rupture of the basement membrane by the cells. The tumors were not considered malignant, even though they were similar to the lesions described by Geschickter, except for the metastases. If the findings of cancer production in species of a non-tumor genetic constitution can be confirmed, the role of the estrogens as etiologic factors may assume greater significance.

Nathanson and Andervont[92] and others,[93, 94] since, have demonstrated that testosterone administered under proper conditions will partially inhibit the appearance of mammary cancer in a highly susceptible strain. This presumably is brought about by an antagonism to the estrogens or by the inhibition of pituitary activity. The hormone, however, has no effect on the tumor once it has developed. Other glands of internal secretion may also be of significance. For example, Cramer and Horning[95] have described a "brown degeneration" in the adrenal which appears to be commoner in the more susceptible strains of mice. Cancer of the breast has also been produced by transplantation of lobes of the anterior hypophysis, but it does not arise in the absence of the ovary.[96] It is now agreed by most observers that at least three factors as suggested by Bittner are necessary for the genesis of breast cancer in the mouse.[89] These are (1) a hereditary influence, (2) the presence of the ovary or its secretions, and (3) the milk factor. All three must be present or cancer does not develop in the experimental animal except possibly in the exceptional case. Moreover, it can be stated at present that the estrogens are not in themselves carcinogenic, but merely provide the substrate upon which an exciting agent may act.

Clinical Aspects.—A study of 2,165 cases of cancer of the breast revealed that the peak of age incidence was reached in the group between 46 to 48 years of age.[97] The median age was 52 years; that is, as many cases occur in patients before this age as after it. About a third of the patients are under 45 years, another third from 45 to 55, and the remainder thereafter. Taylor[35] has compared the time of onset of the disease to the time of the menopause and states that about one-third of the cases occur during the period of mature ovarian function, another third appear within five years before or after the menopause, while the remainder develop in women whose ovarian function has ceased for five years or more. These studies, therefore, are in agreement. It must be pointed out, however, that this represents the age incidence seen in hospitals and is not a true cross section of the entire community. When the incidence in the general population is considered, it has been shown that susceptibility to cancer of the breast increases steadily with age.[97]

It is not known definitely whether women who develop cancer of the breast at any period of life have or have had a higher percentage of menstrual disturbances than those who do not. It has been observed, however, that the menstrual pattern changed shortly before the discovery of the disease.[35] The association of breast cancer with lesions in the pelvis is similar to that observed in other types of breast disease. Taylor noted a fairly close association with tumors of the female pelvic organs suggesting that the entire reproductive system may be subject to the same abnormal stimulus.[98]

It is an accepted fact that nulliparous women have a higher incidence of cancer of the breast than those who have borne children.[99, 100] This is extremely interesting in view of the fact that cancer of the cervix is more common in the multiparous female than the virgin. This situation appears to be the reverse of that found in the experimental animal. The question of lactation is, also, of great interest. It is held by some observers that early weaning of the child or faulty lactation for various reasons conduces to the development of breast cancer.[99-101] This is based on the supposition that atypical lactation results in stasis and breakdown products which may cause chronic irritation, and thus may possibly lead to cancer. Experiments in mice relative to this point have shown that blockage of the mammary ducts with resulting milk stagnation was influential in determining the site and time at which tumors appeared in a susceptible strain, but did not in itself cause an increased incidence.[102] Taylor, in a careful study of approximately 350 children of women with breast cancer, found that 72 per cent were nursed for at least six months; of the remainder a very small number were deliberately weaned and the others were not nursed because of an inadequate milk supply.[35] It would be interesting to know if women with cancer of the breast had normal lactation after every pregnancy. Comparison of the data with normal

women may reveal important information. This problem may now be more easily settled because of the present-day practice of early weaning and suppression of lactation. It is too early to evaluate such material. As pointed out by Taylor, further studies of lactation may be significant because there may be evidence of inflammation resulting from stasis of secretion, or there may be an indication of an abnormal physiologic state, which in itself may predispose to cancer of the breast.[35]

Data in relationship to the menopause are also suggestive. Olch compares the onset of the menopause in normal patients and in those with breast cancer.[103] From his studies, he found that approximately 72 per cent of normal women pass through the menopause at the age of from 40 to 50 years, while 55 per cent of these with cancer are still menstruating at the age of 50. It was concluded that almost five times as many women with cancer of the breast had a delayed menopause as compared to those with a normal climacteric. The average age of the woman in menopause is cited by most observers as 48 years. Since the median age in cancer of the breast is 52 years, one may speculate further on a possible endocrinologic relationship. Inasmuch as disturbed ovarian function is common at the climacteric, it may thus prepare a suitable substrate for the development of the disease. Moreover, tumors which appear later may arise on atypical changes, which originate much earlier. The process described as chronic cystic mastitis may fall into this category. Even though amenorrhea is one of the primary signs of the menopause, the ovary frequently continues to secrete estrogenic hormone in considerable amounts for a relatively long period of time thereafter.[104] In castrate patients and in those many years past the menopause, when all histologic evidence of ovarian activity has disappeared, estrogens are still recovered in the urine. Another probable source of these hormones is the adrenal gland. It is possible, therefore, that stimulation of the breast continues, although it may be entirely different than that in the years when menses are still present.

Development of Carcinoma on Benign Lesions.—The significance of a relationship between certain types of chronic cystic mastitis and carcinoma of the breast is a subject of much controversy. Observations in this regard have been based on the coexistence of the two diseases, the development of cancer in previously proved cystic disease, and the study of changes leading to cancer in the experimental animal and the human being. The important literature concerning this problem has recently been reviewed by Lewis and Geschickter,[105] Warren,[106] and Logie.[107] Of the recent writers, Lewis and Geschickter are not convinced that most types of chronic cystic mastitis are precancerous. Warren and the further statistical confirmation of Logie strongly support the contention of those who postulate a definite causal relationship between the two conditions. The discrepancies may be partly

explained by the criteria set up for the diagnosis of chronic cystic mastitis and the type of material used in the studies. Moreover, in some of the investigations histologic confirmation of the clinical diagnosis was not carried out in all cases. The methods of analysis are also dissimilar. Warren's studies based on histologic examination demonstrate that when age specific rates are used, the breast cancer attack rate for women with chronic cystic mastitis in the premenopausal age group (from 30 to 49 years) is 11.7 times as great as that of the general female population in the same period. Past the age of 50 it is 2.5 times as great and for the entire group 4.5 times as great. Corrections were made for chronic cystic mastitis in the normal population. These findings are significant, since the group with the highest incidence was that in which the ovaries were still active. Therefore, if chronic cystic mastitis is of endocrine origin, then it must be postulated that hormones are responsible at least in an indirect fashion for the development of cancer of the breast.

Hormonal Alteration of Tumors.—

Castration: Herrell[108] reviewed the records of 1,906 patients with cancer of the breast and those of 1,011 without the disease in a similar age group. His findings disclosed that in the cancer group the incidence of complete oophorectomy or castration, before cancer was diagnosed, was 1.5 per cent. The incidence in the noncancer group was 15.4 per cent, or ten times as great. He also suggested that the time of castration was as important as in mice. Schinzinger[109] suggested oophorectomy as part of the treatment of breast cancer. Beatson[110] independently reported several patients who were castrated and noted alleviation of symptoms and signs. Many have since resorted to this procedure and in later years have substituted x-ray for surgical extirpation of the ovaries.[111] Benefits obtained were more striking in the premenopausal group, although even in this group the changes were usually temporary and except in one recorded instance did not show obvious regression of the primary tumor.[112] The greatest changes were noted in the bone metastases, which by x-ray evidence in a fair number of cases regressed or disappeared completely for a time. It has been concluded by those with an extensive experience that castration may be expected to show temporary improvement in about one-third of the patients with recurrent or inoperable cancer, but it cannot be demonstrated as advantageous when employed as a prophylactic procedure in those submitted to radical operation.[113] Farrow and Adair[114] have recently reported a similar experience concerning partial regression of the primary tumor and osseous metastases in a male with cancer of the breast. There can be no doubt that the changes resulted from removal of gonadal secretions. Whether this is the sole factor or whether the changes occur secondarily to an effect on the other glands of internal secretion following castration is a moot question.

The metabolic changes produced by the procedure must also be considered. Regarding x-ray castration, a study in this laboratory has revealed some discrepancy in its efficacy, when compared to the surgical operation.[104] It was found by assays of the urinary estrogen excretion that castration by x-ray, in order to simulate that by operation, depended upon such factors as adequate dosage, size of the portal, and age of the patient. Some patients, although amenorrheic, had a marked fluctuation of estrogens in the urine and in several instances resumed menstruation. Obviously, in this group castration was incomplete, so that results in such cases are equivocal.

Menstrual Cycle: As far as can be determined, there is no effect of the menstrual cycle on the primary tumor. There may be slight gross alterations in size of the tumor, but for the most part this is probably due to vascular change and edema rather than to alteration in epithelial activity.

Pregnancy and Lactation: The rapidity of growth of the primary tumor[115] and the appearance of a tumor in the second breast during pregnancy are well recognized.[116] Changes during lactation are usually even more striking.[115] Whether these effects are due to the hormones elaborated in pregnancy and lactation on the tumor, or to effects on the breast itself is not settled. Taylor and Meltzer,[117] as well as others,[118] contend that the structure of the breast late in pregnancy and during lactation favors development and growth of cancer, particularly with regard to the inflammatory type. This may be due to the increased vascularity which may favor tumor growth, to the richness of the lymphatics which favors dissemination, or to the relative absence of fibrous tissue which removes a natural barrier. These changes may all be produced by hormonal stimulation, but other products of pregnancy may also be responsible.

Effect of Estrogens on the Development of Cancer of the Breast.—Three reports have appeared on the possible development of cancer in the breast after prolonged administration of estrogens.[119-121] There is no proof that this was the direct cause of the tumor, but there is certainly a possibility that it was contributory. With the large numbers of females who are now receiving estrogens over long periods for various endocrine disturbances, particularly the menopause, one would expect the development of more cases if the hormone were directly responsible. However, when the life span, the time, and the dosage required to produce the lesion in a susceptible mouse are translated into human equivalents, it is possible that more cases will appear. In the case of Auchincloss and Haagensen[120] the effect of the estrogens seemed to resemble that seen in the mouse, and was of an unusual histologic type. They have cautioned against indiscriminate use of the hormone over a long period of time or in large doses, when there is a family history of cancer, without initial and repeated examination of both breasts, and in patients with chronic mastitis, cancer, or any form

of neoplasm either before or after surgical or radiation treatment. Such advice is valuable and should be considered by all those who use the hormones.

Effect of Hormones on Cancer of the Breast.—Attempts have been made to influence the course of cancer of the breast by the administration of hormones. We have been unable to demonstrate a direct effect with regard to either augmentation or inhibition of the primary tumor in mouse or man by the administration of estrogens or androgens. Farrow and Woodward[122] have noted that in the premenopausal group skeletal metastases are apt to occur early, whereas, in the postmenopausal group development of skeletal metastases is relatively late. They have also reported a marked acceleration of osseous metastases after intensive androgen or estrogen therapy and have suggested that there may be a direct effect on the secondary deposits themselves. An alternative theory is that these changes are due to an indirect effect which by removal of certain mechanical barriers possibly as a result of altered metabolism permits the metastases to grow unhampered. They, too, have considered this possibility. This is suggested by their observations of a marked decalcification of bone and a rise in concentration of calcium in the serum and excretion in the urine.

Excretion Studies: To date there have been relatively few studies on the excretion rates of the various sex hormones in patients with cancer of the breast. The results obtained thus far may be listed as follows:

Gonadotropic Hormone.—There is no consistent alteration in the excretion of pituitary gonadotropic hormone in patients with cancer of the breast. Zondek[123] has reported an increased excretion of the gonadotropic hormone of placental origin in a pregnant woman with mammary cancer. He was of the opinion that it was due to the cancer as the values fell precipitously after radical operation in the eighth month of pregnancy. This finding in a single case seems to be equivocal.

Estrogens.—Ross and Dorfman[124] made several determinations on each of four patients in the premenopause with breast cancer and could detect no significant variation from normal. These findings have been corroborated by the study of a larger series by Taylor and Twombly[125] and by Nathanson.[126] The latter reported slightly lower values than normally found in some cases, whereas, others had normal or slightly elevated daily levels. In general, there was no deviation from normal, and although the average for the entire group was slightly below that of normal women of the same age, it was not considered significant. The excretion cycle of some of the patients appeared atypical in that the peak of estrogen excretion usually observed at the midmenstruum was either absent or delayed. The significance of such a configuration is equivocal. In cancer of the male breast, Yolton and Rea[127] have reported values comparable to that of normal males of the same age.

ANDROGENS AND 17-KETOSTEROIDS.—Normal androgen values were found by Ross and Dorfman[124] in their series. The excretion of 17-ketosteroids in the patients studied by Taylor and Twombly[125] and by Nathanson[126] were usually within normal range, but in general averages for the groups were slightly lower than those usually found for similar normal individuals. Pearlman[128] has reported a lowered 17-ketosteroid excretion in most patients with any type of cancer; these findings are in accord with those of others.[129] In the cancer of the male breast the 17-ketosteroid excretion has also been reported as normal.[127]

Taylor and Twombly[125] studied the effect of various steroid hormones on the excretion rates of the sex hormones in individuals with and without cancer of the breast. They concluded that there was no striking difference although variations did appear in the cancer patient.

Studies on patients in the menopause with cancer of the breast show essentially the same excretion rates as women in the same period without the disease. Several conclusions may be drawn from these excretion studies. (1) Although variations do occur, there is no significant deviation from normal in the excretion rates of the sex hormones in women with breast cancer. (2) There is no proof that abnormal secretions of the hormones do not accompany or precede the development of the cancer, since excretion levels are not absolute indicators of secretory activity. (3) Carcinoma of the breast may be independent of hormonal influence once it develops. (4) The findings do not prove that the sex hormones are not involved in the disease, but they do indicate that normal excretion values may be found in the presence of the cancer during the period of active ovarian function.

From the foregoing data, it can be concluded that there is no proof that the hormones are the direct cause of carcinoma of the breast. It is possible and likely in some cases that they are indirectly responsible, inasmuch as they may produce precancerous changes or may provide a suitable substrate so that another agent may act.

DISCUSSION

The available clinical and experimental information emphasizes the necessity for the endocrine system in the development and growth of the mammary gland. The ovary and hypophysis are especially important for without one or the other breast development will not occur or will cease entirely. Furthermore, removal of these organs leads to regressive changes in the fully developed breast. Thus, it has been contended that disease of the breast may be definitely related to or caused by alterations of function or secretion of certain of the glands of internal secretion. Factual data, for such a thesis, have been reviewed under each entity. However, a general discussion of the possibilities involved seems necessary since certain factors may be common to all types of breast disease.

Status of the Individual.—Factors other than endocrine must be considered in the development of breast disease. Chief among these are heredity, race, color, and constitutional type. They are frequently interrelated but each may be of special significance. While the evidence to support these possibilities is far from conclusive, one may justifiably speculate on them. The physiologic status of the individual, endocrine metabolism and secretion, and susceptibility to the disease may depend to a considerable degree on these fundamental backgrounds. These basic states in some measure may thus determine the type and degree of response of the organism to normal or superimposed stimuli. This would help to explain the variety of changes in the breast, which have been attributed to the same agent, such as estrogens.

The stage of life and state of the breast when abnormalities appear may, also, determine the type and degree of response to a given stimulus. It has been shown that the diseases which arise during various age periods vary considerably in their histologic structure and clinical manifestations. Moreover, the degree of development and structure of the breast may differ regardless of age as a result of changes in the physiologic status of the individual. Dieckmann[28] has shown that the extent of development of the breast particularly at puberty is subject to wide variation among different individuals. Previous pregnancies and normal and abnormal lactation account for breast changes not encountered in the virgin female. Other conditions, such as inflammatory disease may likewise alter the condition of the breast. Thus, the breast may exhibit wide varieties of histologic structure under different conditions. Hence, these dissimilar substrates may vary considerably in their response to a single stimulus and may determine to some degree the abnormal changes which may appear subsequently.

Character of the Stimuli.—Foremost among the probable stimuli which may be responsible for breast disease are those of the endocrine and nervous systems. The hormones which have been the subject of the most intensive study are the estrogens. Nevertheless, the possibilities suggested by investigations may apply to other hormones as well. How may estrogens produce these atypical states? Several possible modes of action seem tenable. (1) Physiologic amounts of the hormone may act upon tissue which is more sensitive than normal. This susceptibility may be related to the metabolic status of the host, to special characteristics of the cells, or to a change in the breast as a result of the activity of other agents. (2) It has been demonstrated that estrogens are destroyed by the liver. Normal quantities of the hormone may be secreted, but, because of defective function of the liver, abnormal quantities may be released to the tissues. (3) Excessive quantities of the hormone may be responsible, but, except in cancer-susceptible animals, the effects are limited. (4) Atypical hor-

mones may be produced, which may have carcinogenic activity. This is possible since the steroid hormones are closely allied to several of the known synthetic carcinogens. It is conceivable that the formation of carcinogenic agents from hormones may occur as a result of a faulty metabolism due to a change in the physiologic state of the host. (5) Lack of a hormone, which normally stimulates the breast, may lead to degenerative or regressive changes, which might then allow other agents to act.

As has been pointed out, the nervous system may also be involved. The action may be direct, but it is more likely that such stimuli may exert their effect by causing excesses or alterations of hormonal secretion. Then, too, the close interrelation of the various endocrine organs suggests that disturbance of one organ could affect the function of the others. Because of the possible methods of action or alterations of hormonal secretion, there is still lack of conclusive evidence to justify the acceptance of any one factor.

Endocrine Dysfunction.—In almost all types of breast disease from the simple infantile hypertrophy to the complex breast cancer, there is a suggestion of some dysfunction of the endocrine system in many of the cases. Thus far, the evidence has been confined almost entirely to clinical observations. To recapitulate, the relatively high incidence of atypical menstrual cycles, of disease of the female pelvic organs, of abnormalities of lactation, the fertility of the patients and the number of pregnancies, the time of life at which the various processes appear, and the accentuation or regression of several types of lesions after the appearance or removal of obvious stimuli is sufficient to point to the endocrine organs as possible etiologic factors. In the experimental animal, also, there are apparent differences in the endocrine constitution of the low and high mammary tumor strains. Some have reported differences in the estrous cycles, the fertility, changes in the breast following pregnancy, the histologic appearance of the glands of internal secretion (particularly the ovary and the adrenal), the response to known stimuli, and the time of life under identical conditions at which the tumors appear. The effect of one endocrine organ upon another must also be given serious consideration. Such analogies between men and animals are dangerous in drawing conclusions. Nevertheless, it can be stated at present that in either case there is no evidence to support the thesis that the hormones in themselves are directly responsible for the production of neoplastic disease. It is possible, however, that they may be the exciting factors in the production of precancerous lesions and in this fashion may contribute to the development of the malignant process.

Significance of Hormone Excretion.—Urinary excretion levels of the sex hormones represent only the end products of metabolism. It has not yet been proved, whether or not they give a true index of the

blood levels, the rate of secretion or destruction, or the utilization of the hormones by the tissues. Furthermore, they do not reveal the exact nature or relationship of the various components of the hormones excreted. Recent data from isolation studies suggest that patients with cancer may excrete estrogens[130] and 17-ketosteroids,[129, 131] in a different fashion from individuals without cancer. The usual relationship of the individual components of both the estrogens and 17-ketosteroids may be atypical, as well as the normal ratio between the total estrogenic and 17-ketosteroid complexes.

It is clear that alterations in excretion levels or the specific type of hormone isolated are not necessarily characteristic for patients with cancer. They may merely represent deviations from normal, which may occur only as a result of disturbed metabolism in the sick individual. They indicate, however, a distinct abnormality and as such are significant in the study of the disease.

Similarity of Lesions of the Breast.—As was previously suggested, the state of the breast at the time that an abnormal stimulation may be superimposed is probably of some importance. Infantile and virginal hypertrophy, early ripening, gynecomastia and mastitis in the male, and possibly adenofibrosis are remarkably similar in histologic appearance and in their resemblance to changes usually seen in the normal adolescent female. It is conceivable, therefore, that they may be due to the same etiologic agent, possibly the hormones. Lewis and Geschickter[132] have emphasized this similarity with respect to virginal hypertrophy, gynecomastia, and fibroadenoma, and there is fairly good evidence to support it. The different forms of cystic disease also basically resemble each other, in spite of considerable variation in the individual case. Each type may represent a further stage of a similar process. The more advanced forms such as Schimmelbusch's disease may conduce to, precede, or accompany carcinoma of the breast.

CONCLUSIONS

1. The endocrine organs and their secretions are necessary for normal growth, development, and maintenance of the mammary gland. As such, they are indirectly responsible for breast disease, inasmuch as they provide the tissue in which the lesions arise.

2. Factors such as heredity, constitution, race, color, and physiologic state of the individual must also be considered as etiologic factors in breast disease.

3. The state of the breast at the time of onset of disease seems to be an important factor in the type of lesion seen. A single stimulus may thus produce a variety of differently appearing lesions.

4. Localized tissue susceptibility may account for an unusual response to what may appear to be a normal stimulus.

5. Endocrine dysfunction is frequently associated with and may be responsible for certain benign lesions, but there is no absolute proof that it is the only or direct etiologic factor.

6. Hormones may possibly be the direct cause of malignant change in the breast either from an excess stimulation, or as a result of an atypical metabolism. As yet, there is no concrete evidence to prove this. It is more likely that they merely prepare a substrate upon which another agent may act.

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THE EFFECT OF SEX HORMONES ON SKELETAL METASTASES FROM BREAST CANCER

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IN THE medical literature there are reports of almost every type of human cancer metastasizing to the skeletal system. It is well known, however, that cancers originating in certain organs rarely metastasize to bone while others seem to have a selective proclivity for the osseous parts. This peculiar variation does not seem to be determined by the simple laws of chance or the proximity of the primary growth to the bony structures; it suggests contributing factors of local and systemic origin. From an endocrinological viewpoint it appears especially significant that the two primary cancers most frequent to metastasize to bone arise in the breast and prostate, organs whose development and functions are closely allied with the metabolism of sex hormones. Hence, among the many measures tried to control primary and metastatic cancer of the breast and prostate is the artificial production of a hormone imbalance.

An investigation of the effect of ovarian estrogens and testicular androgens on mammary cancer and its metastases to bone presents a most complex problem, one subject to many controversial opinions as well as conflicting clinical data. It is therefore necessary to preface this presentation with certain fundamentals in order to facilitate a systematic review and an intelligent interpretation of the variable results.

First, the ovaries and the testes are a part of the endocrine system. The organs of this system and their individual products show a remarkable degree of normal variation as well as multiplicity of effect, and yet by an integral relationship with each other maintain a hormonal balance to which the system tends to revert. Hence, any natural or artificial disturbance of this balance, caused by either the menopause or castration, will be followed by compensatory changes in other endocrine organs and a partial replacement by hormones or compounds having a biologic effect similar to that of those which have become deficient. Thus, Woolley, Fekete, and Little[1] report a nodular hyperplasia of the adrenal cortex and subsequent proliferation of the mammary epithelium following castration of both male and female mice. Furthermore, in an extensive review of experimental work, Riddle[2] notes that hormones capable of producing growth of the breast tissues have been found not only in the ovary but in the pituitary, adrenal,

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and testes. Other experimental data indicate that an excess of sex hormones, whether due to a natural overactivity of the ovaries or testes or to artificial stimulation by prolonged administration of synthetic hormone preparations from these organs, will be similarly compensated by a degeneration of other parts of the endocrine system. Such artificial stimulation is apparently a stronger influence for compensatory action than a natural overactivity.

It follows that any imbalance due to excesses or deficiencies of sex hormones may be of a temporary nature.

Second, it is generally accepted that susceptibility of response to stimulation by a specific hormone involves a hereditary factor as well as time and a suitable environment. Furthermore, experimental and clinical data have demonstrated that susceptibility varies in different species, individuals, and individual organs, and that to some extent it is proportionate to the amount of hormones present. Hence the results of a sex hormone imbalance will be inconsistent.

It is proposed in this discussion to describe the effect of producing a sex hormone imbalance by the following methods: (1) withdrawal of ovarian estrogens; (2) addition of synthetic ovarian estrogens; (3) addition of synthetic testicular androgens; and (4) withdrawal of testicular androgens.

WITHDRAWAL OF OVARIAN ESTROGENS

An evaluation of any effects due to a deficiency of estrogens during the natural menopause is difficult because the time and duration of the menopause vary in different patients. Furthermore, there is no agreement as to the exact time of the onset of the hormone imbalance or its duration. Hence, in analyzing a series of cases any effects observed may be expected to involve a period of several years.

In a previous report[3] a tabulation of the age incidence in 200 instances of skeletal metastases occurring in 1,380 cases of breast cancer was made. During the years of the natural menopause (41 to 55) there was a noticeable decrease in the percentage of skeletal metastases, while a relatively high percentage occurred just before and after the years covering this time. From this evidence it was concluded that in the natural course of events skeletal metastases may be delayed but not prevented by the endocrine disturbance of the menopause.

Beatson[4] introduced the artificial menopause as a means of controlling advanced mammary cancer when he performed bilateral oophorectomies on two patients. This method of producing a hormone imbalance by the sudden withdrawal of ovarian estrogens was practiced for a limited time by other surgeons. In 1905, Lett[5] published an analysis of ninety-nine cases of breast cancer in which the patients were treated by this procedure. He reported clinical improvement with evidence of arrested disease activity in 41.3 per cent of the patients who were 50 years of age or less, but noted marked palliation in only 23.2 per cent of the entire group.

The discovery that ovarian sterilization could be produced by pelvic irradiation added a more simple and less hazardous means of producing an artificial menopause. While such a procedure has been used extensively one finds surprisingly few patients treated entirely by this means. Most of the literature on this subject indicates that castration was supplemented by irradiation of the local lesions. The recorded results are therefore difficult to analyze. The reports of Dresser,[6] Taylor,[7] Smith,[8] and Martin,[9] however, have emphasized the production of temporary arrests and the calcification of skeletal metastases from breast cancer by pelvic irradiation.

Although a considerable number of castrated patients have been personally observed, no attempt to give detailed figures will be made because of the usual complicating factor, namely, supplementary irradiation to most of the local lesions. In general it is believed that about one-third of the patients in premenopause will be materially benefited by castration. Evidence of this benefit is usually first manifested by a rather prompt relief from pain and general physical improvement. Calcification of the skeletal metastases, generally regarded as indicative of a regressive process, can be demonstrated radiographically in three to six months. In advanced cases where there is hypercalcemia, the accompanying symptoms of nausea and vomiting usually subside rather quickly and this subsidence may be correlated with a decrease in the serum calcium.

The duration of inhibited activity in the skeletal metastases varies considerably but usually is from six to twenty-four months. In a rare case it may last longer. Thus, Clarkson and Barker[10] report a remarkable case. After five years their patient was clinically well and the previously involved bones showed an essentially normal texture. Castration, however, had been supplemented by intensive irradiation of the widespread skeletal metastases.

The possible mode of action is extremely interesting although many factors are as yet unknown. There is some reason to believe that the recognized vasodilating action of estrogenic hormones may be an important factor. As an example, the following case is cited.

CASE 1.—In August, 1940, Mrs. E. W., aged 45 years, came to the hospital with an inoperable breast cancer which had been present for one year. Metastatic nodules had been appearing in the skin of the breast during the previous four months. The menstrual history was normal; periods began at the age of 14 years, were always regular and occurred every twenty-eight days with the flow lasting four days. An examination of the left breast showed a hard, infiltrating tumor, measuring 6 by 8 by 4 cm., centrally located and with an extension upward toward the axilla. The nipple was fixed and retracted. The skin overlying the tumor was infiltrated with cancer. Surrounding this area there were numerous cutaneous metastases which had a dusky red color. A pelvic examination revealed a slight symmetrical enlargement of the uterus. Biopsy of one of the skin lesions was reported, "Infiltrating small cell diffuse mammary carcinoma, Grade IV."

Treatment.—The patient was treated solely by ovarian irradiation. This was begun Aug. 14, 1940, and completed eight days later. Using 200 kilovolts, ½ cm. copper filter, 70 cm. skin target distance, 500 roentgens were given daily to one of four pelvic fields for a total of 1,000 r to each area.

Clinical Observations.—During the month following pelvic irradiation she had a scant menstrual flow on three occasions. Then she began having fairly severe menopausal symptoms and had no further menstrual bleeding. There was a gradual decrease in the hyperemia of the cutaneous nodules. This was later followed by their shrinkage and at the end of ten months the nodules were barely palpable.

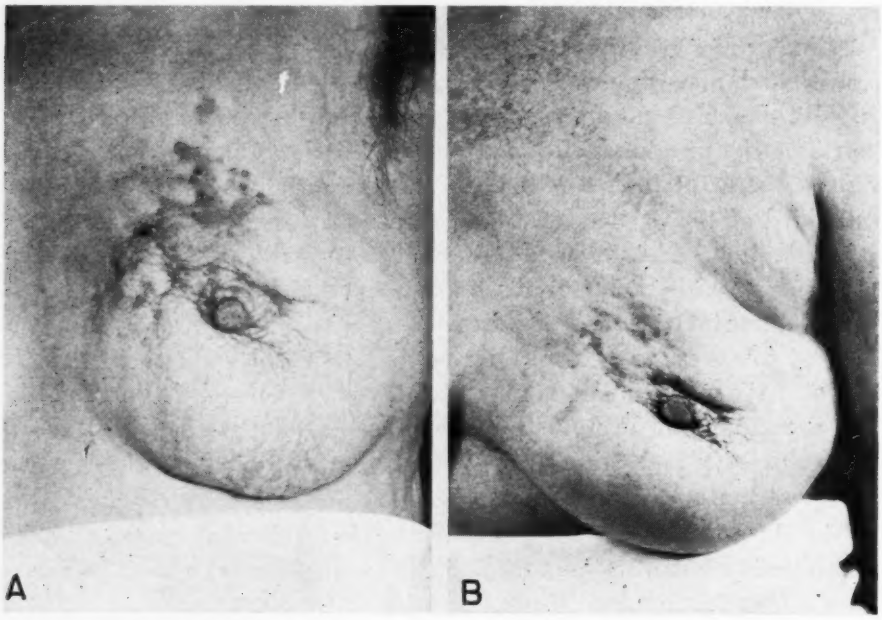

Fig. 1 (Case 1).—*A*, Photograph taken shortly after menstruation ceased because of pelvic irradiation; *B*, 16 months later. Note disappearance of cutaneous nodules and marked decrease of lymphoedema of skin of breast.

One year following castration axillary nodes could not be definitely felt and the mass in the breast was estimated to be about one-third of its original size. She had gained considerable weight and had no symptoms suggestive of distant metastastes. The last clinical examination nineteen months after castration revealed evidence of renewed disease activity by the appearance of two new skin nodules.

The pertinent points were a visible loss of vascularity of the lesions and their gradual shrinkage until no longer palpable. Skin nodules for histologic studies were removed 26, 71, and 234 days following castration. All of them showed apparently unaltered cancer cells, although the lesions were decreasing in size. From this evidence it is believed that the regression was due mainly to vasoconstriction causing a nutritional anemia and abortive fibrosis. Although no similar studies have been made on skeletal metastases following castration, I have made certain observations which lend some support to this view. First, osteoplastic lesions from breast cancer rarely appear in the premenopausal group unless the patient has been sterilized. Second, it

has been noted that osteolytic lesions occurring in vascular bones such as the ribs, vertebrae, and pelvis show comparatively early calcification after castration whereas those of the shaft of the long bones may show only minor changes. Moreover, in comparing the rate of calcification of medullary metastases with the clean-cut or "punched out" cortical ones, it is apparent that those in the medullary part of the bone show increased density more rapidly.

ADDITION OF ESTROGENS

There is a wealth of excellent experimental data in the literature on the appearance of breast cancer in both male and female animals after the administration of estrogenic substances. Fortunately, the number of reported cases of human cancer which follow or at least appear in time after the injection of female sex hormones is limited. The reports of Auchincloss and Haagensen,[11] Allaben and Owen,[12] and Parsons and McCall[13] are cautious in their conclusions but certainly warrant the timely editorial of the *Journal of the American Medical Association*[14] warning against the indiscriminate use of estrogenic substances for mammary disease.

There are surprisingly little experimental data on the effect of estrogenic substances on an established cancer in animals. Haddow,[15] after a limited number of observations in mice, reports no inhibition of growth.

For clinical data one can always bring forth the much discussed and controversial question of the effect of pregnancy on breast cancer. The reports are confusing, mainly because the material is limited and no one has observed a sufficient number of untreated breast cancers associated with pregnancy to warrant conclusions. There is certainly no evidence that pregnancy inhibits the growth of cancer. Smith,[16] from studies at the Memorial Hospital, did not believe that pregnancy materially influenced the course of breast cancer. Riach,[17] Rosenthal,[18] and Emge,[19] from much less clinical data, believed that pregnancy definitely accelerated the growth of breast cancer in their cases. The report of Egoville[20] is of particular interest. His patient, aged 30 years, had as her first symptom pain in the back beginning in the sixth month of pregnancy. Clinical and radiographic examinations demonstrated a cancer of the breast with widespread bone metastases. Studies of the blood showed a serum calcium level of 18.7 mg. per 100 c.c. The patient failed rapidly and died.

I have observed the effect of estrone on skeletal metastases from breast cancer in only three instances. Unfortunately for purposes of present analysis, these patients had previously received large doses of testosterone propionate. Therefore, the clinical value of this report is greatly reduced and requires further substantiation. The doses of estrone administered parenterally were relatively small. One patient was

given 2 and 4 mg. while the remaining two had only single doses of 2 mg.

The case here mentioned will illustrate the elevation of the serum calcium following injections of estrone as well as testosterone propionate.

CASE 2.—Oct. 21, 1939, Miss L. L., aged 26 years, was admitted to Memorial Hospital. She complained chiefly of a severe and persistent pain in the thoracic spine of two and one-half months' duration. For one year she had been aware of a small growth in the right breast. There had been a weight loss of seventeen pounds but no other associated systemic disturbances. Menses were regular with the flow lasting about six days. An examination of the right breast revealed a 4 by 3½ by 2½ cm. tumor. It was located in the upper central portion of the breast. In the adjacent midaxilla there was a metastatic node 1 cm. in diameter. Roentgenographic studies demonstrated osteolytic lesions in the ribs, spine, cranium, and pelvic bones. Aspiration biopsy of the breast tumor was reported cancer.

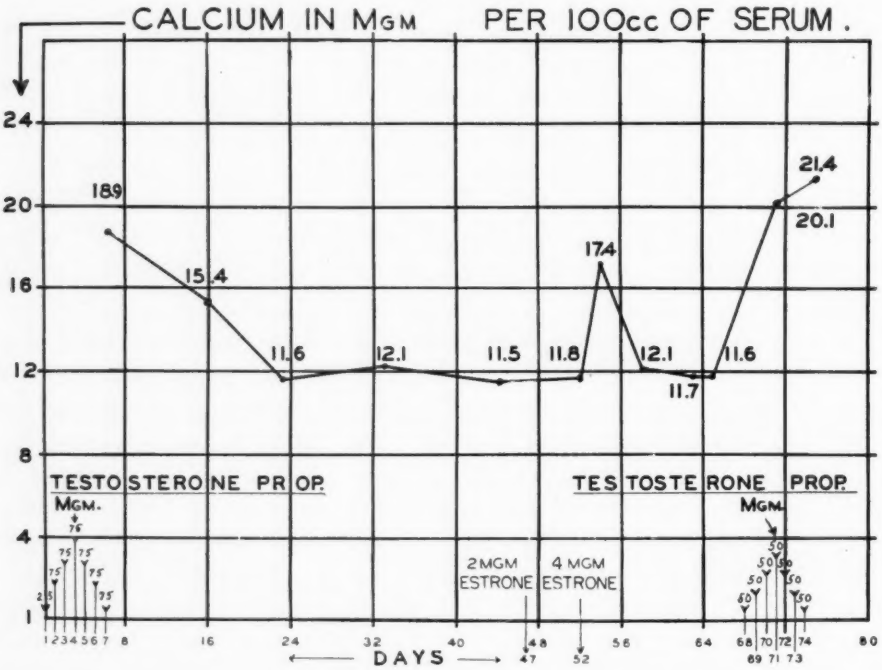

Fig. 2 (Case 2).—Demonstrating the elevation of the serum calcium following injections of testosterone propionate and estrone.

Treatment.—The patient was admitted to the Memorial Hospital and 25 mg. of testosterone propionate in 1 c.c. of sesame oil were injected into the gluteal muscle. During the following six consecutive days the dose was increased to 75 mg. daily, making a total of 475 mg. in seven days. Six weeks later she was given 2 mg. of estrone in oil intramuscularly and after an interval of five days an additional 4 mg. Nine days later a second series of testosterone injections was started, 50 mg. daily being given for a total of seven doses.

Clinical Observations.—After each series of injections the patient suffered from nausea and vomiting which subsided a few days after discontinuing the administration of the hormones. In general the clinical course of this patient was one of progressively failing health owing to widespread and uncontrolled metastatic disease. She died Jan. 17, 1940.

Of particular interest was the appearance of hypercalcemia (Fig. 2) after each series of hormone injections. During the period of observation a slight increase in the size of the breast tumor was noted. Roentgen studies demonstrated a striking increase in the extent of the osteolytic metastases in the ribs, spine, and pelvic bones.

Concerning the effects of estrone as well as testosterone it is assumed with probability that the resulting hypercalcemia was due mainly to an increased activity of the metastatic tumor in the skeletal system. This in turn caused an acceleration in the rate of bone destruction accompanied by a flooding of the circulation by the products of osteolysis.

Not infrequently one is faced with the problem of giving estrogens to postmastectomy patients who are suffering from menopausal disturbances. While there is no clinical evidence to contraindicate estrogenic therapy in the absence of disease, it is highly important to consider the possibility of activating a quiescent and unrecognized focus of metastatic cancer. In general it would be much safer to forbid pregnancy or the use of estrogens in all cases of mammary cancer for at least five years and preferably longer.

ADDITION OF ANDROGENS

It has been only within the past five years that the production of the primary male sex hormone, testosterone propionate, has been sufficient to permit experimental and clinical use. During this time there have been reports stressing the inhibitory action of this substance on the growth and function of the mammary gland.

The effect of testosterone on breast cancer has received only limited attention. Nathanson and Andervont[21] found that when testosterone was given to mice of the C3H strains at an early age it prevented the development of spontaneous tumors. They added, however, that no effect could be observed on the growth of a tumor already present. More recently, Loeser[22] has reported that the implantation of testosterone pellets in mice of the Strong A strain reduced the mortality from spontaneous cancer from 75 per cent in the controls to 40 per cent in the treated animals.

Loeser[22] also reports on the use of testosterone in five human beings with cancer. Three of these were said to be free of disease at the time the pellets were implanted and remained well for almost four years. In two cases where disease was present no regression of the cancer was observed although systemic improvement and relief of pain were noted.

Beginning in 1939, a series of thirty-three patients having bone metastases from breast cancer was given doses of testosterone propionate varying from 5 to 25 mg. in sesame oil for totals of six to twelve doses. All of these patients are now dead. Temporary relief from pain with some general improvement was noted in about one-half of the cases. No case showed clinical or radiographic evidence of disease control.

Later three females and one male were given large doses of testosterone propionate. A complete report[3] has been published on the three female patients. One of these cases has already been cited elsewhere in this article. The remaining two women were aged 37 and 60 years, respectively, and had developed bone metastases after radical mastectomies. The younger of these two patients was given 400 mg. of male sex hormone at the rate of 25 mg. twice daily. By the fifth days after the injections the serum calcium had risen from an initial level of 11.6 mg. to 15.4 mg. The other patient received two 25 mg. ampules of testosterone daily for ten days. Her serum calcium increased from 10.2 to 14.2 mg. Both patients also received 2 mg. of estrone several weeks after the injections of the male sex hormone. This too was followed by a similar but less marked hypercalcemia. The clinical course of the two women was relatively the same. Both failed rapidly and died. X-ray studies of the bones revealed further extension of previous metastases and the appearance of numerous new ones.

The fourth case, that of a male, is briefly summarized below.

CASE 3.—In May, 1939, Mr. J. S., aged 63 years, applied to the Memorial Hospital for treatment of a progressive swelling of the left breast of ten months' duration and persistent pains in the right thigh for the previous three months. An examination of the left breast demonstrated an ulcerating cancer, centrally located and measuring 4.5 cm. in diameter. A hard metastatic node having a diameter of 3.5 cm. was present in the adjacent axilla. X-rays of the pelvis showed osteolytic metastases in the upper right femur. Biopsy of the breast lesion was reported, "Adenocarcinoma—tubular duct, Grade II."

Treatment consisted of high voltage x-ray therapy to the breast, axilla, and right femur. Later a palliative simple mastectomy was performed. Pains in the hip were immediately relieved but recurred within seven months. He was readmitted to the hospital and given daily injections of 50 mg. of testosterone propionate for seventeen consecutive days except for two days when 100 and 75 mg. were given. A total of 925 mg. was administered during the seventeen days.

Clinical Observations.—The pains were not relieved. He complained of nausea on several occasions but suffered no vomiting. Following discharge from the hospital pain became more severe and on the thirty-fourth day after hormone therapy x-ray studies of the skeletal system indicated widespread metastases. Previously seen foci had shown marked extension and numerous new areas were present. Subsequently x-ray therapy was given with only slight relief. Prior to death ten months later he suffered numerous pathologic fractures.

The main points to be emphasized are a rapid extension of preexisting skeletal metastases and the appearance of numerous new ones. Although there were no marked blood chemical changes, hormone studies of the urine during the time of treatment showed an increase in the output of estrogens (34.0 to 50.0 M.U.) and of androgens (44.5 to 56.7 mg.).

From this evidence it is apparent that the administration of large doses of synthetic androgens not only failed to inhibit the growth of metastatic mammary cancer but seemed to increase its activity in the skeletal system in both sexes.

WITHDRAWAL OF TESTICULAR ANDROGENS

Male breast cancer is relatively uncommon, comprising about 1 per cent of all mammary cancers. From collected reviews,[23-25] however, it is apparent that there are no recognized histologic differences and the clinical course is relatively the same in both sexes.

Mainly because of the sequence of events described in Case 3 another male with breast cancer with skeletal metastases was treated by castration. Since it is to be reported elsewhere only a brief summary follows.

CASE 4.—M. S., aged 72 years, applied to the Memorial Hospital on April 28, 1941. Four months previously he had noticed an ulceration of the left nipple. This had not only refused to heal but had become larger. An examination revealed an ulcerating cancer which had destroyed the nipple. It measured 5 by 4 by 2½ cm. and was movable. Several nodes were palpable in the left axilla,

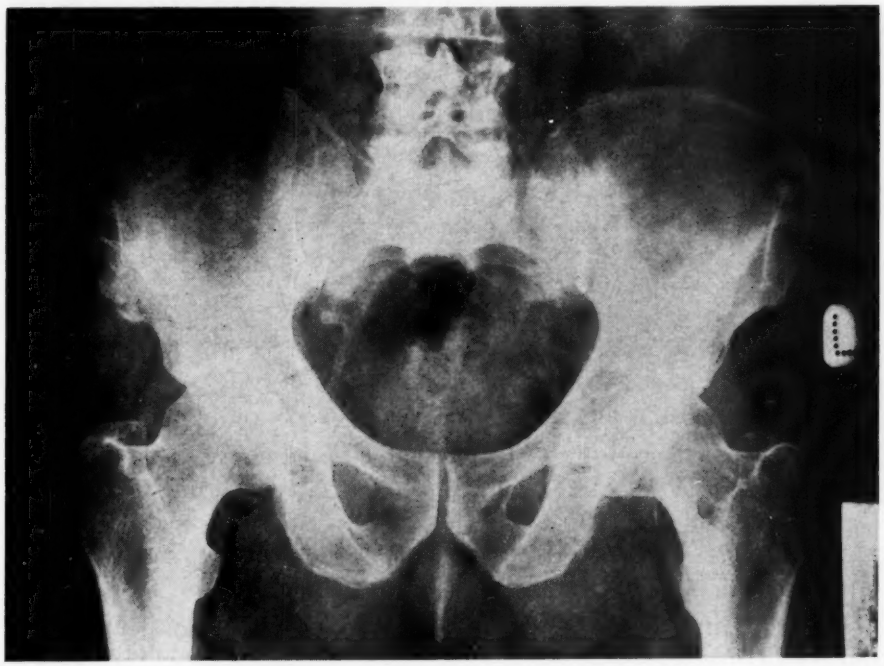

Fig. 3 (Case 4).—Roentgenogram demonstrating osteolytic metastases in the right ilium and pubic bones as well as the fourth lumbar vertebra.

the largest of which measured 1 cm. in diameter. The chest plate was negative. A radical mastectomy was advised but refused by the patient, who did not return to the hospital until nine months later. During the interval there had been a definite increase in the size of the local lesion. For several weeks he had suffered persistent pains in the right chest and the back. X-rays showed numerous metastases in the ribs, spine, pelvis, scapula, and skull. There was also fluid in the left pleural cavity interpreted as indicative of probable pulmonary metastases. A biopsy of the breast lesion was reported, "Infiltrating mammary carcinoma, Grade II."

Treatment.—The patient was admitted to the hospital and a bilateral orchidectomy performed Feb. 9, 1942.

Clinical Observations.—Relief of pain was almost immediate. Subsequent clinical and radiographic examinations have revealed a regression of the breast tumor with partial healing of the ulceration and also an increased density of the preexisting skeletal lesions. The latter was most marked in the ribs, ilium, scapula, and lumbar vertebrae. The fluid in the left pleural cavity had disappeared.

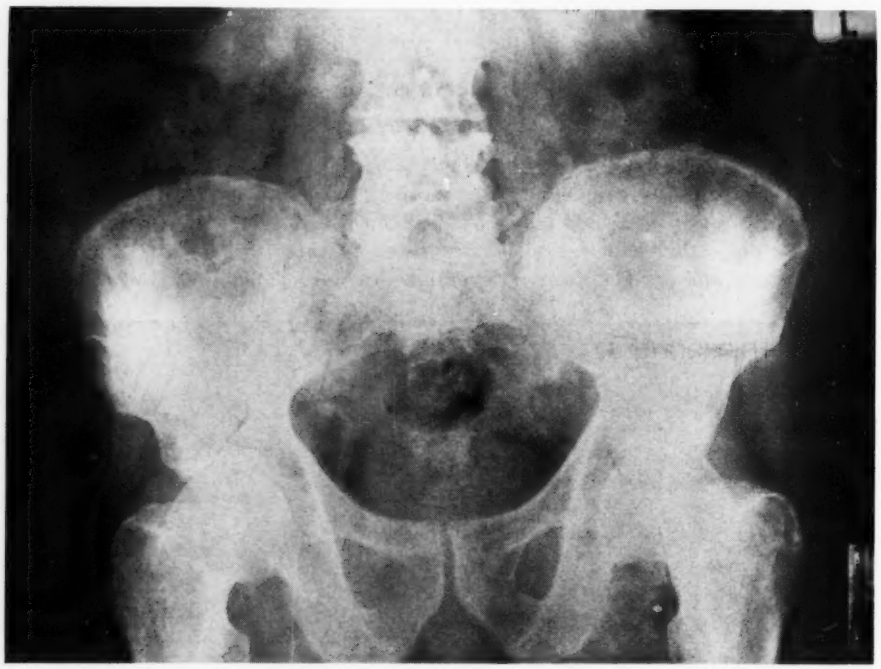

Fig. 4 (Case 4).—Roentgenogram taken four months following castration. Note increased density of metastatic foci in the right ilium and fourth lumbar vertebra.

Blood chemical studies on this patient revealed no significant changes except an elevation of the acid phosphatase from 0.15 to 1.0 units. Hormone analysis of the urine indicated a decrease in the estrogen excretion from 22.5 to less than 4 M.U. while the output of 17 ketosteroids remained fairly stable.

While the interval of four months does not permit any definite conclusions, the evidence at hand indicates a regression of both the local lesion and the osseous metastases. It is highly probable that this is temporary.

CONCLUSIONS

At present any attempt to describe the possible effect of natural or synthetic endocrine products on the growth of primary or metastatic breast cancer means merely the recording of one or several observations. The fact remains that present knowledge is far from complete. To summarize, it appears that estrogens and androgens have a similar effect on skeletal metastases from mammary cancer. The evidence at this time indicates growth inhibition in certain cases following a withdrawal of either of these hormones. Conversely, an excess of either

seems to accelerate the rate of growth. Furthermore, it is highly probable that the observed effects are inconstant and of a temporary nature.

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BENIGN HYPERTROPHY AND CARCINOMA OF THE PROSTATE

Occurrence and Experimental Production in Animals

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THE basic observation that the testes control the development and state of the secondary sexual organs was made at some time early in the history of man's contact with domesticated animals, either accidentally or deliberately. The farmer used this information in the castration of roosters to produce capons, with their supposed greater weight and more delicious meat. Castration of other animals was also found to be useful to the agriculturist. In man, the Turks and Chinese took advantage of the suppression of secondary sexual characters and sexual drive by orchiectomy in prepuberal boys to supply the eunuchs for the harems. Religious sects, such as the Scopzen in Russia, used gonadectomy in the male to depress sexual drive after the thirty-fifth year of life as a part of their taboo. Incidentally, the operation of ovariectomy was beyond their ability, so that the comparable procedure in women was to sew the labia almost closed and burn the nipples.

Scientific study of the phenomenon of atrophy of the secondary sexual characters after the removal of the testes was initiated by John Hunter, who noted among other things that the prostate underwent progressive atrophy. This knowledge of a general biologic principle was put to little practical use in the treatment of disease in man until the end of the nineteenth century, when White proposed that castration be used to induce atrophy of the enlarged prostate of older men. Within the last few years Huggins and his associates have shown that the testes in some way influence the growth of prostatic carcinoma, and that removal of them results in considerable clinical improvement.

It is the purpose of this communication to present the evidence for and against the concept that benign hypertrophy and carcinoma of the prostate are endocrinologic dystrophies, and to review the occurrence and experimental production of the two conditions in animals.

Evidence That Benign Hypertrophy of the Prostate Is an Endocrinologic Dystrophy

Age Incidence.—Benign hypertrophy of the prostate is characteristically a disease of men over the age of 40 years. Few if any patients with true nodular hyperplasia have been observed before this age. Most

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instances of prostatism in younger men are the result of acute prostatitis or of hypertrophy of the median bar of muscle at the internal urethral orifice. In my own series of over 700 prostates studied microscopically, the youngest individual with a true nodule formed within the prostatic tissue was 39 years of age, and the nodules in this case were microscopic in size. With increasing age there is an increasing incidence of benign hypertrophy, until 75 per cent of all men from 80 to 90 years of age have histologically demonstrable nodules within the gland (Moore). In contrast with this, the clinical incidence of urethral obstruction demanding operative interference reaches a maximum at about the age of 63 years (Gover). It is possible that patients older than 63 years are not subjected to operative removal of the enlarged prostatic tissue, but a number of urologists have told me that this cannot be the entire explanation. In terms of the etiologic agent these figures mean that the causal agent is present after the age of 40 years, that it reaches its greatest intensity at the age of about 60 years, and decreases in intensity thereafter, but remains active in the production of additional and new nodules.

Racial Incidence.—A difference in racial incidence does not of necessity mean that a disease is caused by a hormonal dystrophy, but it does establish a constitutional difference. In contrast with the figures noted for the Caucasian race, benign hypertrophy of the prostate, both clinically and pathologically, is a rare disease among the Chinese people (Chang and Char). Comparative figures are 45 to 55 per cent of all Caucasian men over 40 years of age, and 6 per cent of similar Chinese men. Char* informs me that he has no explanation of this difference except one of constitution. It is true that Buddhist religion prohibits sexual intercourse after the age of 35 years, but it is improbable that this is held to by all Chinese people, and as will be explained in the next paragraph this could not account for the entire difference. In contrast, hypertrophy of the prostate in Negroes is as common as in the white man (D'Aunoy, Schenken, and Burns; Derbes, Leche, and Hooker).

Marital State.—According to the extensive investigation of Gover, benign hypertrophy of the prostate is slightly less common in single men than in married men, when the marital state of patients with the disease is compared with the marital state of the population in general. This difference is significant, with a probable error in excess of 4. Young suggests that benign hypertrophy is a rare disease in the Catholic hierarchy, but Dr. Edward L. Keys of New York informs me that he has seen many priests of the Catholic Church with the condition, and believes that it is as common in them as in the general population.

Constitution.—There are no precise scientific studies on the relation of constitution to the incidence of benign hypertrophy. It has been suggested that men whose constitutions tend toward the feminine type—that is, men with broad hips, prominent breasts, inconspicuous sexual hair,

*Professor of Urology at the Peking Union Medical College.

and loose inguinal rings—develop benign hypertrophy more frequently than others (Moszkowicz). Draper found that individuals with benign hypertrophy had longer ears than any other group of individuals with disease. There is a single report of the occurrence of benign hypertrophy in identical twins in the same year of life (Kaufmann).

Retention of Exogenous Creatine.—It has been postulated that the retention of ingested or injected exogenous creatine is an index of the state of androgenic stimulation. Studies of young individuals, older men without disease of the prostate, and older men with prostatic hypertrophy reveal no difference in the retention of exogenous creatine. By injection of androgens into all of these individuals there is increased retention, indicating that the tissues are still responsible to the androgenic hormones (Sutton).

The Effect of Castration.—At the end of the nineteenth century White proposed that since the prostate undergoes atrophy following castration, the enlarged prostate should also undergo atrophy. The procedure was carried out on a large number of patients, but the evaluation of the results became so controversial that it is not possible at the present time to evaluate them with any accuracy. In the original report by Young on perineal prostatectomy, there are descriptions of the prostates of two individuals subjected some years before to castration. The typical hyperplasia of the epithelium and of the stroma is described in both. The slides on the case reported by Nancrede have been kindly reviewed for me by Dr. C. V. Weller,* and his description is typical of benign hypertrophy without evidence of atrophy. Similarly, in one case in the files of the New York Hospital, I have not been able to find any evidence that castration brings about atrophy of the hyperplastic tissue. More recently, Deming, Jenkins, and van Wagenen came to the same conclusion. Deming has been good enough to allow me to examine the sections, and I fully agree with his interpretation. In contrast, Huggins and Stevens have examined two enlarged prostates several months after castration, and in one case found atrophy of the epithelium and of the stroma. Huggins has given me slides from this case, and I find myself in full agreement with his interpretation. It is entirely possible that a few patients respond and that most do not. Certainly the subject is worthy of further investigation.

The Effect of Hormones.—Most reports of the study of tissues in prostatic hypertrophy following the injection of androgens leave no doubt that these substances have no effect on the histologic appearance of the hyperplastic tissue (Moore and McLellan; Draper, Slaughter, and Denslow; Heckel). There is a single report that additional hyperplasia was present (Keller and Hull). With estrogens there are the typical changes resulting in all animal species: metaplasia of the urethral and ductal epithelium and increase of lymphoid tissue (Moore and McLellan). In-

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vestigators at the Cleveland Clinic, working under the general direction of Lower, found that castration in rats resulted in atrophy of the prostate and hypertrophy of the pituitary gland. Injections of androgens restored the prostate to normal but had no effect on the pituitary. On the other hand a water-soluble extract of the testes induced atrophy of the prostate but restored the pituitary to normal. They therefore postulated that the testes contained two hormones, one fat-soluble and one water-soluble. Feeding of the latter substance to patients with benign hypertrophy resulted in clinical improvement in about 60 per cent. Reed Nesbit* has been good enough to allow me to examine sections from the prostates of two men who received this treatment for over one year and then had prostatectomy. There is in these slides no evidence of atrophy.

Relation to the Pituitary Gland.—The theories developed by Lower and his associates postulated a hyperactivity of the pituitary gland. In order to secure information on this point I have studied the pituitaries upon which the reports of Parsons and of Melchionna and Moore were based. Together these constitute 150 glands. As shown in Table I there is no difference in the weight of the pituitary gland in men with clinical benign hypertrophy, and in men without disease of the prostate of a comparable age group.

TABLE I

WEIGHT OF PITUITARY IN RELATION TO BENIGN HYPERTROPHY OF PROSTATE

TYPE OF PATIENT	NUMBER OF OBSERVATIONS	AVERAGE WEIGHT OF PITUITARY (MG.)
Men over 40 without benign hypertrophy	16	644
Men over 40 with benign hypertrophy	20	627
Women over 40	23	751

In contrast, the pituitary gland of women over the age of 40 years is considerably heavier. Histologic study for the presence of adenomas, for basophilic invasion of the posterior lobe, and for gross changes in the relative proportion of the cells reveals no relation of any of these conditions to benign hypertrophy of the prostate. The reverse relation of the state of the prostate in disease of the pituitary gland is also of interest. There are a few examples in the literature of complete destruction of the pituitary by a suprasellar cyst, producing pituitary infantilism. Histologic examination of the prostate shows complete atrophy, and in those patients who have lived to be over 40 years of age there is no evidence of benign hypertrophy. In the carefully studied cases of acromegaly reported by Cushing and Davidoff there is note of hyperplasia, but not of the formation of nodules. There are inadequate reports in the literature of patients with basophilism and of patients with Sim-

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monds' disease to arrive at any conclusion concerning the nature of prostatic changes.

Urinary Excretion of Hormones.—Although there is not entire agreement, most reports indicate that there is a slight to moderate decrease in the urinary excretion of androgens and estrogens in the urine of patients with benign hypertrophy as compared with individuals of similar age (Moore, Miller, and McLellan; Dingemanse and Laqueur). In contrast with the greatly increased excretion of prolan in the urine of postmenopausal women, there is no increase in men, either with or without benign hypertrophy (Woodman and Stimpel).

Lipopenia.—In most patients with benign hypertrophy there is a 30 to 40 per cent decrease in the total lipid, total cholesterol, cholesterol ester, and phospholipid in the blood. This is interpreted as evidence that the condition is a general metabolic disturbance (Boyd and Berry).

Part of the Prostate Involved.—The smallest and presumably the earliest lesions of benign hypertrophy of the prostate are found in the periurethral tissue cephalad to the distal end of the verumontanum. Similar small lesions are also seen about the prostatic ducts of the lateral and middle lobes, and occasionally within the lobules of the lateral lobes. Nodular hyperplasia is never observed in the posterior lobe. In pseudohermaphrodites the structure of the prostate is dependent on the sex of the gonad. If there are ovaries present, the prostate is represented only by the middle and lateral lobes; while if testes are present the entire male prostate, including the posterior lobe, surrounds the urethra (Moszkowicz). These observations indicate that the middle and lateral lobes of the prostate constitute an ambisexual organ, while the posterior lobe is a distinctly male structure. Comparison with the distribution of benign hypertrophy of the prostate further indicates that this disease involves the ambisexual part of the prostate—in other words, that part which is sensitive to both androgens and estrogens. This conclusion is further supported by a study of the prostate of the newborn infant, which is presumably exposed to excessive amounts of estrogen crossing the placenta from the blood of the mother. In the prostate of the newborn infant there is squamous metaplasia within the urethra, about the verumontanum, and in the ducts to the lateral and middle lobes (Diaca; Brody and Goldman).

Relation of the Adrenal.—For many reasons it has been supposed that some activity of the adrenal gland is the cause or one of the causes of benign hypertrophy. It is known that the adrenal gland of the young rat is capable of maintaining the normal appearance of the prostate for as long as 40 days in both male and female animals (Price). In a qualitative study of the excretion of urinary androgens in the urine of patients with benign hypertrophy, Miller found that there is a relative increase in the amount of dehydroisoandrosterone, and a relative and absolute decrease in the amount of androsterone. Callow and Callow

and others have shown that the source of dehydroisoandrosterone in man is probably the adrenal gland; it remains after castration but disappears from the urine in diseases involving destruction of the adrenal cortex. Despite this inferential evidence of the relation of the adrenals to benign hypertrophy, no morphologic changes have been described. It is possible that more precise studies with differential staining of the androgenic cells would give a positive answer to the question. On the contrary, morphologic studies of the prostate in diseases of the adrenal gland have shown a definite relation. In the rare adrenal insufficiency of young children with hypertrophy of the adrenal glands (Dijkhuizen and Behr), there is hyperplasia of the prostate to the point where it is identical in structure with that of the adult. I have had an opportunity to study two of these cases;* both patients died of adrenal insufficiency. At autopsy the adrenal glands were twice normal size, and the prostate showed a typical adult structure. Unfortunately, no studies for fuchsinophilic granules were made in either case. These observations do indicate, however, that the androgenic activity of the adrenal gland may be considerable. This conclusion is supported by the enlargement of the prostate in patients with a functioning tumor of the adrenal cortex. Of great interest would be studies of the female prostate in young girls with virilism and with an adrenal tumor. Despite the most assiduous search, I have not been able to find any published reports on this point. It has been shown by a number of investigators that the injection of androgenic hormones into female rats will result in great hyperplasia of the vestigial prostate in about 25 per cent of animals (Korenchevsky; Korenchevsky and Dennison; Hamilton and Wolfe). I have been able to study† the prostate in 15 cases of Addison's disease, 12 resulting from tuberculosis and 3 from primary cortical atrophy. In none did the prostate differ from the expected structure, and we must therefore conclude that the androgenic and estrogenic activity of the adrenal in adults is not of sufficient intensity to affect the structure of the prostate.

Recurrence.—The phenomenon of recurrence following a so-called prostatectomy is a well-recognized phenomenon. It indicates nothing more than that this operation involves removal of only the enlarged tissue, and that the basic cause of the disease remains. The average interval between the first and second operation is about 5 years, although periods as short as 2 and as long as 10 years have been reported (Kretschmer).

Effect of the Operations of Steinach.—According to the experimental results of Steinach, ligation and division of the vas deferens in an adult animal organism will result in hyperplasia of the interstitial cells of the testes and rejuvenation of the maleness of the organism. Under the assumption that benign hypertrophy of the prostate results from a de-

*One at the New York Hospital under Dr. Oscar Schloss, and one at the St. Louis Children's Hospital under Dr. Alexis Hartmann.

†Through the courtesy of Dr. Shields Warren, Dr. H. G. Wells, and Dr. Douglas Symmers.

creased excretion of androgen, the Steinach II has been employed in the treatment of the disease. The results are comparable to all other methods of treatment; namely, about 50 to 60 per cent are improved (Jacobs). It is highly improbable that this improvement represents a specific effect of the ligation of the vas. Clarke has clearly shown that rest in bed, catheterization, or any other well-recognized conservative treatment will give improvement and relief of symptoms in patients with prostatic hypertrophy for periods of years.

Relation to the Testes.—Morphologic studies of the size and structure of the testes in patients with benign hypertrophy of the prostate have uniformly shown that there are no consistent alterations associated with this disease. Specifically there are no changes, either qualitatively or quantitatively, in the interstitial cells. The direct effect of castration on the development of disease has been discussed. The problem may, however, be approached in another way. In the medical literature there are careful pathologic reports, including microscopic description of the prostate of 28 eunuchs, eunuchoids, or individuals with pituitary infantilism who lost the secondary sexual characteristics before the age of 40 years and lived to be over 45 years of age. These include every report that could be found, and it is hoped a summary may be published soon. There is not a single example of benign hypertrophy in this group. In the population at large, similar studies would reveal that 50 per cent had evidence of nodular hyperplasia. It is highly unlikely that the absence of the condition in 28 consecutive cases of men over the age of 45 could be chance observation. We may hence conclude with statistical support that benign hypertrophy does not develop except in the presence of a functioning testis—the strongest evidence yet offered that the disease is an endocrinologic dystrophy. In fact it is positive evidence, which cannot be disputed. In patients with a teratoma of the testis in whom there is a large amount of prolan in the body fluids and in the urine, there are no consistent changes in the prostate. Certainly there is no hyperplasia. This commonly occurs in young individuals during the third decade of life, and the prostatic acini are normally lined with tall, columnar epithelium, a point overlooked by some investigators of this subject who have reported hyperplasia. In the few reports of interstitial cell tumors of the testes, hyperplasia of the prostate is noted, but it is never nodular in distribution, but rather diffuse and of the same character seen in children given large amounts of androgens.

Metabolism of Surviving Tissue.—Surviving slices of the tissue involved in benign hypertrophy show a type of respiration similar to that of actively growing tissue, that is, a significant Pasteur effect. Whether or not this can be interpreted as evidence that benign hypertrophy is a tumor depends on the evaluation of the entire principle of Warburg. Attempts to influence the prostate of the rabbit with hormones so that a

similar type of metabolism results have not been successful (Tolins and Moore).

Chemistry of Prostatic Secretion.—Differential chemical analyses of the lipids in prostatic secretion of young men and of older men with and without benign hypertrophy show no significant differences (Moore, Miller, and McLellan).

Summary.—The great mass of data indicates that benign hypertrophy of the prostate is an endocrinologic dystrophy. The nature of the dystrophy is not clear, but it seems certain that it is not an excessive amount of any type of hormone, but rather is a shift in the relative amounts of the various androgenic and estrogenic substances. Present evidence indicates a decreased excretion of biologically active androgen, a less striking decrease of estrogen, and a relative increase of the adrenal androgen, dehydroisoandrosterone. This, in general, means a relative estrogenic and adrenal androgenic preponderance, acting on the ambisexual part of the prostate.

OCCURRENCE OF BENIGN HYPERTROPHY OF THE PROSTATE IN ANIMALS

Dogs.—About 80 per cent of dogs over the age of 8 to 10 years show enlargement of the prostate. This is frequently referred to as benign hypertrophy, but in my opinion there is no evidence that the disease in dogs and in man are the same. Histologically, in a dog the hyperplasia is diffuse and rarely if ever occurs in the form of nodules. In the large series of canine prostates studied by Zuckerman and McKeown there was not a single example of nodular hyperplasia. Dr. William H. Feldman of the Mayo Foundation has sent me a representative group of prostates from older dogs, used in the study of Schlotthauer. In none of these were there nodules. It is possible that the etiologic factors are the same in man and in the dog, but the response on the part of the tissues is different—in the dog, diffuse hyperplasia, and in man, nodular hyperplasia. The general structure of the canine prostate is similar to that of man, and aside from monkeys this species seems the best experimental animal for investigation.

Monkeys.—So far as I am aware there are no reports of nodular hyperplasia of the prostate in older monkeys, but this means little. Most monkeys employed in the laboratory are less than 3 years old, and have not yet gone through puberty. It is to be hoped that the colony in Puerto Rico will furnish a number of older monkeys, comparable in age to the man of 60 or 70 years of age. Until these studies are carried out, no statement concerning the natural incidence of prostatic disease in the monkey can be made.

Rat.—The rat has served for most of the experimental studies on the sex hormones. There is a single case report by Deming, Jenkins, and van Wagenen of a nodular type of hyperplasia in the suburethral tissues of the rat. The appearance shown in their published photomicrographs is not similar to that of the human disease.

Other Species.—In one lemur, Fox reported a papillary adenoma of the prostate. H. N. S. Green (personal communication) states that he has seen one typical nodular hyperplasia of the prostate in a rabbit, but both the tissues and the record were lost, unfortunately.

EXPERIMENTAL PRODUCTION OF BENIGN HYPERTROPHY OF THE PROSTATE

There are no convincing reports in the medical literature that a condition identical or even similar to benign hypertrophy has been produced in experimental animals. The injection of androgens leads to diffuse hyperplasia. The injection of estrogens leads to metaplasia and some hyperplasia of tissues about the urethra. In neither are nodules formed of either stroma or epithelium. These results indicate that the problem is far more complex than the simple injection of excessive amounts of one hormone. Our own experiments have been directed toward the implantation of pellets of various hormones into castrated animals, in an attempt to reproduce approximately the hormonal status of men with the disease. This involves injection of androgen at a submaintenance level, the injection of sufficient estrogen to be just in excess, and the injection of dehydroisoandrosterone in amounts from 5 to 10 times that of the active androgen. The results have so far been negative. We have also attempted to bring about nodular hyperplasia by periodic injections in castrated rats. Adult animals were given 1 mg. once every 10 days for periods up to 180 days. In 3 there was suggestive encapsulation of lobules of the prostate, but not sufficiently clear to claim reproduction of the disease.

EVIDENCE THAT CARCINOMA OF THE PROSTATE IS AN ENDOCRINOLOGIC DYSTROPHY

Age Incidence.—Carcinoma of the prostate is a distinctive tumor in that it is definitely a neoplasm of increasing age. There are not over 25 cases in the world literature of carcinoma of the prostate in individuals less than 30 years of age (Joeck). It has been established that after the age of 40 years there is a gradual decrease in the urinary androgens which are biochemically active. As the urinary androgens decrease there is a progressive increase in the incidence of carcinoma of the prostate, until during the eighth decade it is one of the most important and frequent of all carcinomas (Duff).

Racial Incidence.—Although racial incidence does not prove that a tumor is related to hormones, it does demonstrate a constitutional or genetic factor which may in turn control the endocrine status. In Chinese people, carcinoma of the prostate is a rare form of tumor, and in the series studied by Hu and Ch'in there was only one instance of carcinoma of the prostate in 379 carcinomas in Chinese men.

Incidence in Eunuchs and Eunuchoids.—To my knowledge there is not a single instance in the literature of the occurrence of carcinoma of

the prostate in a eunuch nor in a true eunuchoid. The criteria for the eunuchoid state are the changes in the secondary sexual organs, and not the fact that the testes are small. It has been repeatedly demonstrated that there is no correlation between the size of the testes and the strength of the secondary sexual characteristics nor the excretion of urinary androgens.

Effect of Irradiation of the Testes.—Irradiation of the testes leads to marked atrophy of the seminiferous tubules, and to slight atrophy of the interstitial cells. There is an associated decrease in urinary androgens. According to the report of Munger, patients with carcinoma of the prostate given 500 R. of irradiation by high voltage x-ray to each testis did better and survived in a higher percentage than the patients treated only by resection. There is not, however, the striking effect observed after castration, and irradiation of the testes cannot be recommended as an alternate therapeutic procedure at the present time.

The Effect of Castration.—This topic is completely covered by Dr. Charles Huggins in another article of this symposium, and will not be discussed here.

Effects of Estrogens.—By serial biopsy, Schenken and Burns demonstrated that the administration of stilbestrol over periods up to 60 days brought about profound degenerative changes in the neoplastic cells of carcinoma of the prostate.

Effects of Androgens.—At the time of this communication there are no histologic studies to demonstrate the effect of androgens on carcinoma of the prostate, but in 3 cases reported by Huggins, Stevens, and Hodges there was an increase of pain in the legs and an increase of the serum acid phosphatase following the administration of testosterone propionate. In one case studied by Moore and McLellan an individual with carcinoma of the prostate was given 600 mg. of testosterone propionate over a period of 12 days. The histologic appearance of this carcinoma was not significantly different from the usual carcinoma of the prostate. The man died with multiple metastases 12 months after a radical perineal prostatectomy.

Acid Phosphatase.—An acid phosphatase most active at a pH of 5 is present in prostatic tissue in small amounts during infancy and childhood, and in large amounts after puberty (Moore and Hanzel; Gutman and Gutman). This observation clearly indicates that secretory activity and adulthood in man are directly related to the amount of acid phosphatase in the prostate. Experimental support is given by the demonstration that the low prepuberal levels in the monkey may be promptly increased by injections of testosterone propionate (Gutman and Gutman). In patients with carcinoma of the prostate and metastases to bone there is a remarkable increase in the acid phosphatase of the serum (Gutman and Gutman; Robinson, Gutman, and Gutman; Barringer and Woodard). Castration or injection of estrogens will cause a decrease in

the serum acid phosphatase, while injection of androgens results in a further increase (Huggins and Hodges). The excessive phosphatase is readily demonstrable in histologic sections of the neoplastic tissue (Huggins, Stevens, and Hodges).

OCCURRENCE OF CARCINOMA OF THE PROSTATE IN ANIMALS

In sharp contrast with the situation in man, carcinoma of the prostate is apparently rare in all animals except the dog. This rarity may be only apparent, because most of the animals that have been studied are domesticated by man and are sacrificed as a source of food during what amounts to childhood. Wild animals brought into captivity in most instances do not live a full lifetime.

Primates.—Of all of the monkeys, chimpanzees, and other primates studied in the laboratory during the past 100 years, there is only a single observation of a primary carcinoma of the prostate. This was noted in an old monkey *(Rhesus mulatta)* of unknown age, by Engle and Stout.

Dogs.—Many dogs live for over 10 or 12 years, yet there are relatively few observations on carcinomas of the prostate. Sticker collected the autopsy material on dogs from Berlin Veterinary Institute and the Dresden Veterinary Institute. In Berlin there were 1,306 autopsies on dogs, with 72 tumors, of which 11 were primary in the prostate. The youngest of these 11 dogs was between 6 and 8 years of age. Of 111 tumors in dogs observed at the Dresden Institute none were primary in the prostate. In a summary of his own observations and those recorded in the literature, Sticker noted 11 carcinomas of the prostate among 956 carcinomas of dogs. Krause observed a carcinoma of the prostate or urethra in a cryptorchid dog. Folger, in a review of tumors in animals in 1917, could find only 5 reports in the European literature of carcinoma of the prostate in dogs. They were all adenocarcinomas. Feldman, in his survey of neoplasms in domesticated animals in 1932, gave no added examples of citations from the literature. In their critical study of the prostate in 243 dogs of all ages, Zuckerman and McKeown found one carcinoma of the prostate in a dog with an adenocarcinoma of the testis. It is their opinion that this association was probably fortuitous. Of 15 dogs with adenocarcinomas of the testes, the prostate in 5 showed advanced squamous metaplasia of the glandular system, an indication of powerful estrogenic stimulation. In this series of 243 dogs, 89 were estimated to be 6 years of age or older. In view of the high incidence of latent carcinoma of the prostate in man (Moore; Rich), 15 to 20 per cent, it is significant that no latent carcinoma of the prostate was found in these older dogs.

Other Species.—Sticker observed 110 tumors in bovines, with 1 carcinoma of the prostate. Among 509 tumors in horses, again there was only 1 carcinoma of the prostate. McCoy examined about 100,000 wild rats and found 103 primary tumors, none of which originated in the

prostate. Sticker observed no carcinoma of the prostate among 21 carcinomas in the cat. Among the many reports by Slye and her co-workers there is no mention of carcinoma of the prostate. One sarcoma of the seminal vesicle in a mouse was observed. In connection with the experimental production of so-called squamous-cell carcinoma of the prostate with estrogens, it is significant that of 153 nonexperimental squamous-cell carcinomas in mice, none was primary in the prostate (Slye, Holmes, and Wells). Among 94 tumors of captive wild animals Fox reported no carcinoma of the prostate, but one papillary adenoma in a ring-tailed lemur *(Lemur catta)*. So far as I am aware no carcinoma of the prostate in the rabbit or in the guinea pig has been recorded.

EXPERIMENTAL PRODUCTION OF CARCINOMA OF THE PROSTATE IN ANIMALS

By Injection of Androgens.—In spite of the evidence in man that carcinoma of the prostate is improved by orchidectomy, and made worse by the injection of androgens, there are no reports of the production of carcinoma of the prostate in animals by injection of androgens. These studies include those of Rössle and Zahler on adult dogs and of Zahler on senile dogs. In both instances the period of study was relatively short, and the amount of androgen given was probably inadequate. Zuckerman and Parkes injected 242.5 mg. of testosterone propionate into a castrated rhesus monkey during 91 days. The histologic structure of the prostate was normal. In lemurs, up to 1,985 mg. in 157 days gave only diffuse hypertrophy and hyperplasia (Zuckerman and Sandys).

By Injection of Estrogens.—Lacassagne, Lacassagne and Villela, and Burrows and Kennaway independently observed that long-continued administration of estrogen brought about pronounced squamous metaplasia of the epithelium of the prostate of the mouse. This has frequently been referred to as a squamous-cell carcinoma, but there is no evidence that the cells take on neoplastic potentialities. From my own experience, based on observations on 6 mice and 3 rats given 250 international units of estradiol benzoate weekly for 173 days, there was nothing more than metaplasia. The basement membrane was sharp and there was no invasion of the surrounding stroma by epithelial cells. A similar change occurs in the rhesus monkey, and here the greatest degree of hyperplasia of cells and metaplasia of epithelium is in the utricular bed (Zuckerman). Two Hanuman lemurs given 287.2 and 121.5 mg. of estrone for 483 and 316 days, respectively, showed no evidence of carcinoma. There was only excessive epithelial hyperplasia in the prostatic utricle and in the prostatic ducts (Zuckerman and Sandys). In rabbits administration of estrogens for short periods of time bring about squamous metaplasia of the urethra about the orifice of the seminal vesicles, and migration of polymorphonuclear leucocytes in large numbers through the metaplastic epithelium.

By the Use of Carcinogenic Chemicals.—Carcinoma of the prostate does not result from the application of carcinogenic chemicals onto the skin, or injection into the subcutaneous tissues. Moore and Melchionna have studied the effect of benzypyrene dissolved in lard injected directly into the prostate of the white rat. After 110 days, tumors were found in the prostate, and previous castration had no appreciable effect on the time of appearance or incidence of tumors. Both squamous-cell carcinoma and leiomyosarcoma were observed. In animals over 500 days of age and in animals injected with testosterone propionate the incidence of tumors was somewhat higher, but the experiments did not encompass a sufficient number of animals to justify definite conclusions. The whole problem of the relation of hormones to experimental carcinoma in the white rat is now under investigation in this laboratory.

SUMMARY

1. There is inferential evidence but no definitive proof that benign hypertrophy and carcinoma of the prostate are in part caused by an imbalance of the endocrinologic status of the patient.

2. Benign hypertrophy of the prostate is apparently a distinctive disease of man. An exactly analogous lesion has not been observed in animals, but observations on animals of comparable age are limited in number.

3. Carcinoma of the prostate occurs in dogs and rarely in other species. Occult carcinoma of the prostate, a common lesion in older men, has not been observed in animals, in spite of investigation of suitable specimens.

4. Benign hypertrophy of the prostate has not been produced in experimental animals.

5. An adenocarcinoma of the prostate similar to that in man has not been produced in experimental animals. The injection of the carcinogen, benzpyrene, results in the formation of squamous-cell carcinoma and sarcoma.

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Book Review

The Modern Management of Colitis. By Jacob A. Bargen, M.D., Chief of the Section on Intestinal Diseases, Mayo Clinic, Rochester, Minn. Ed. 1. Pp. 322, with 148 illustrations. Springfield, Ill., 1943. Charles C Thomas, Publisher. $7.

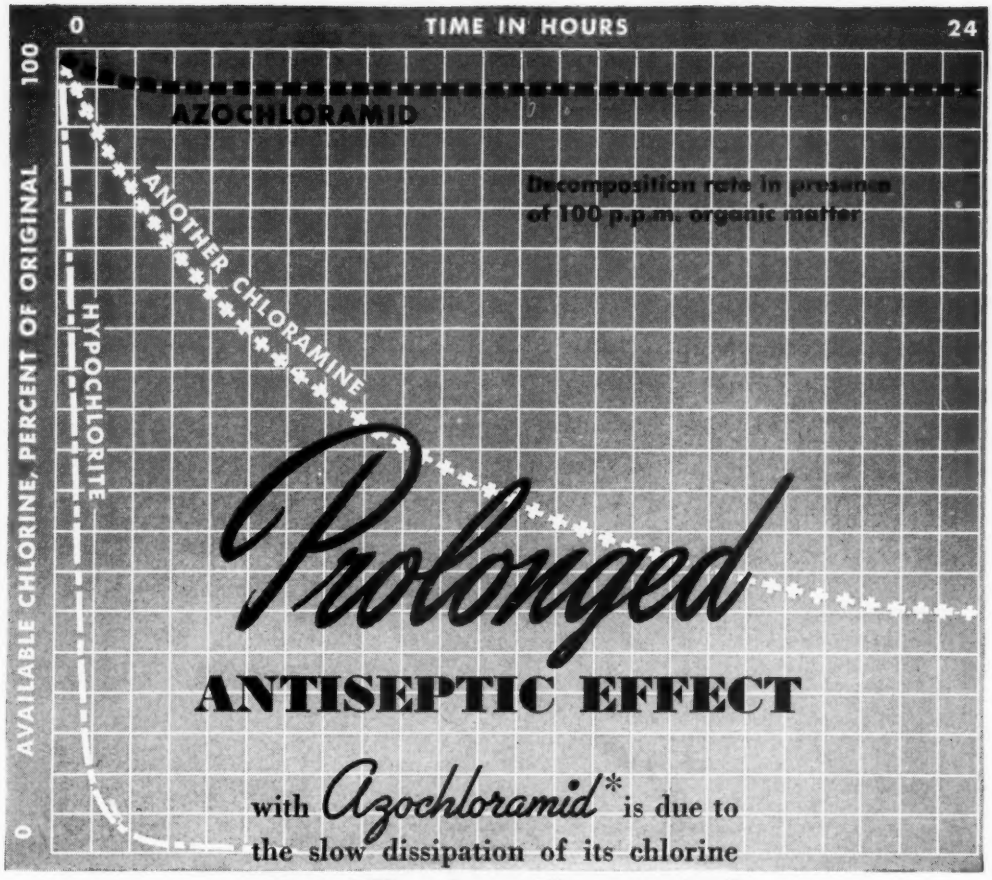
The author of this book is well known for his work on ulcerative colitis. This volume is essentially an attempt to summarize the author's broad experience in that field. Whereas other conditions, such as the irritable colon, allergic colitis, "deficiency colitis," regional colitis, lymphogranuloma venereum, tuberculosis, and amebic colitis, are all dealt with in a brief manner, it is with the many manifestations of so-called chronic ulcerative colitis that the author is especially concerned in this treatise. Bargen recognizes the following types of chronic ulcerative colitis:

1. Thrombo-ulcerative colitis of streptococcal origin, constituting approximately one-half of all observed varieties of all types of colitis. The entire colon is involved.

2. The regional or segmental type with rectum uninvolved, the most favorable type in that surgical excision may be performed.

3. A type which the author designates "chronic ulcerative colitis"—a division about which the author probably is somewhat confused, for in attempting to characterize it, he says, in part, concerning its proctoscopic appearance: "The gross appearance of the interior of the bowel may be considered 'typical' because of its 'atypical appearance.'"

The author regards Type I, thrombo-ulcerative colitis, as being primarily a medical disease and employs ileostomy only as a last resort in these cases—a conclusion which he appears able to justify by an analysis of the Mayo Clinic experience. The author regards ileostomy as inevitable in Type III. There are a large number of cases cited depicting the various types of disease described. The illustrations (largely roentgenograms, are satisfactory and a list of eighty-five references is appended. The monograph may be recommended enthusiastically as summarizing the author's rich experience in a chapter of medicine that is not particularly bright and in which more illumination and enlightenment are needed.



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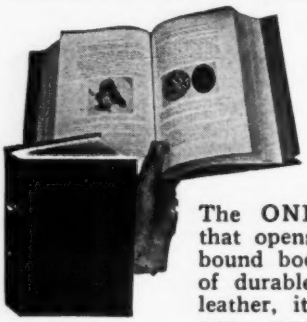

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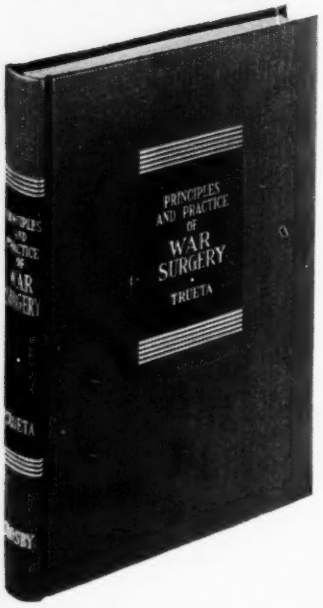

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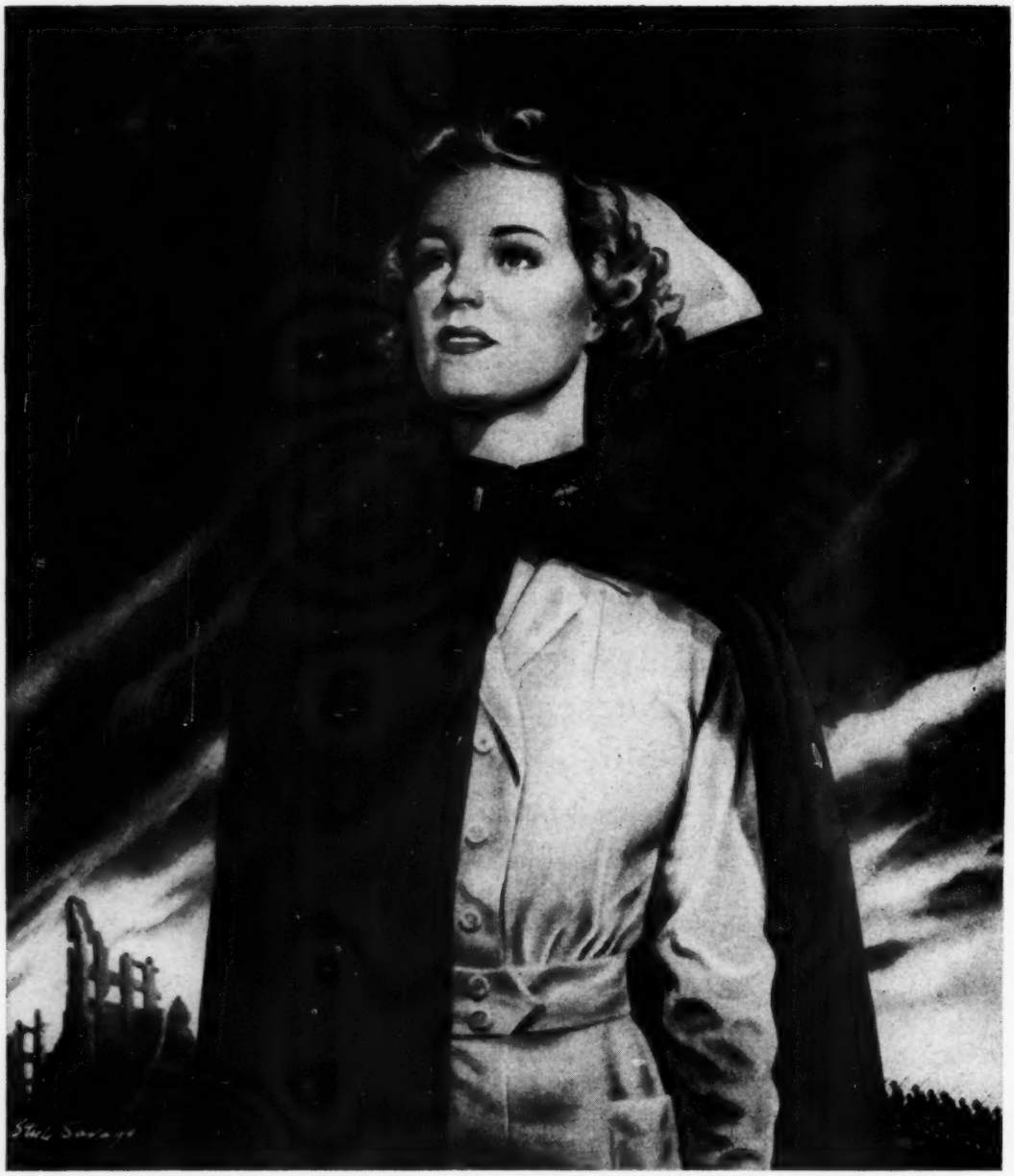

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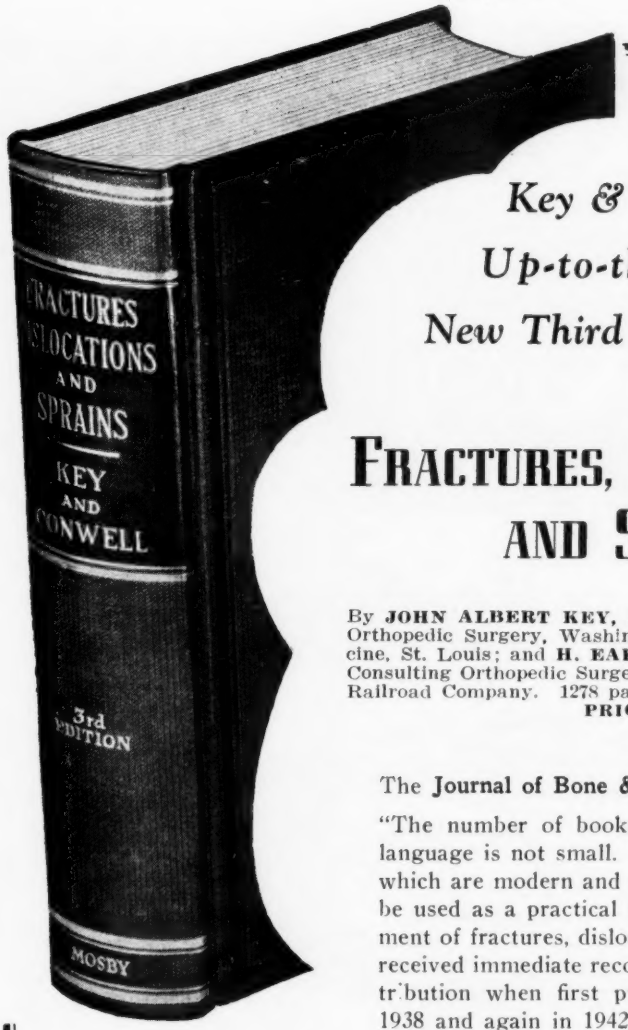

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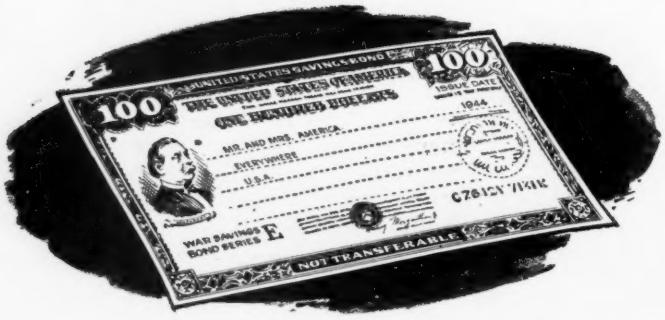

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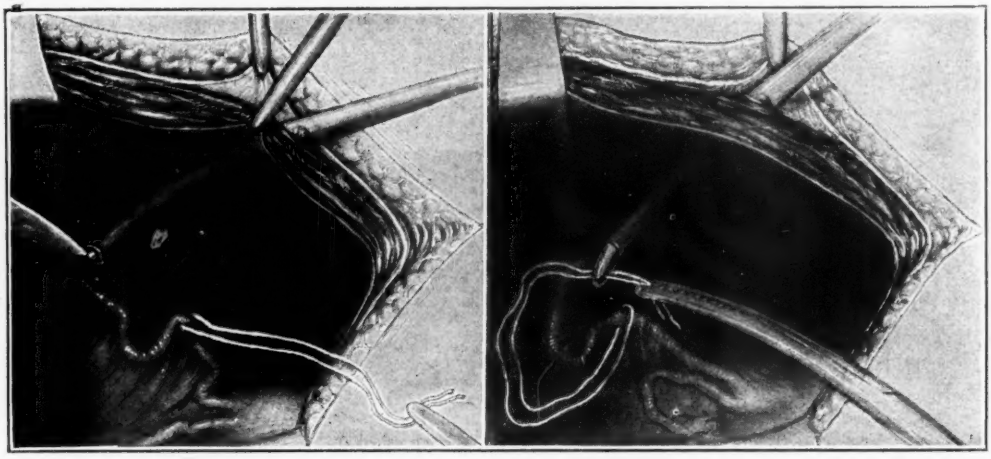

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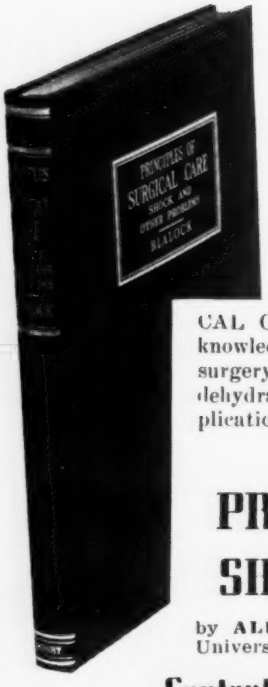

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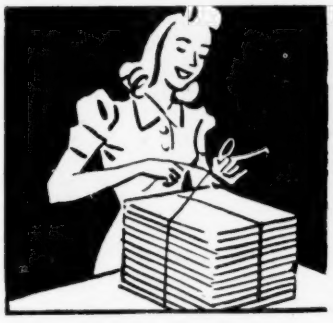

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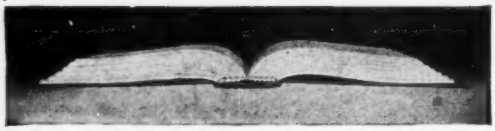

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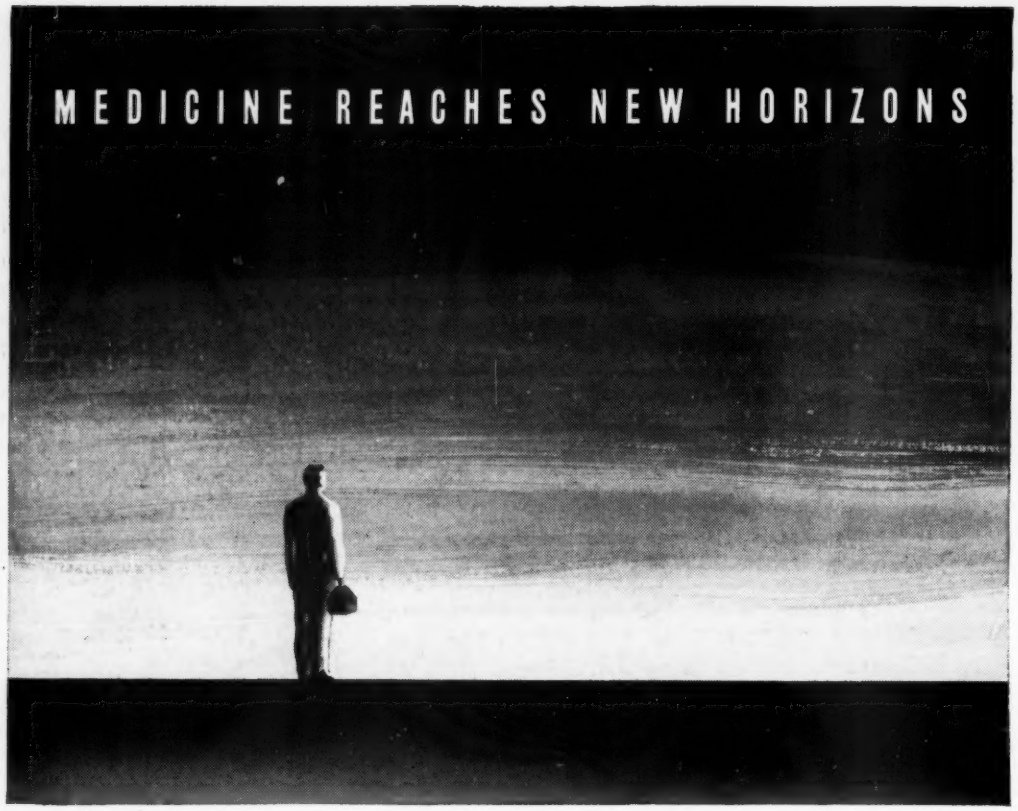

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